Appeal No. 16-2281

United States Court of Appeals

for the

Federal Circuit

eRESEARCHTECHNOLOGY, INC.,

Plaintiff-Appellant,

– v. –

CRF, INC. d/b/a CRF HEALTH

Defendant-Appellee.

Appeal from the United States District Court for the Western District of Pennsylvania in Case No. 2:15-cv-00918-NBF, Judge Nora Barry Fischer

PRINCIPAL BRIEF OF APPELLANT
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September 6, 2016

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, counsel for Appellant certifies that:

1. The full name of every party represented by the undersigned counsel in this case is: eResearchTechnology, Inc.

2. Name of Real Party in interest (only including any real party in interest NOT identified in Question 3) represented by me is: eResearchTechnology, Inc.

3. Parent corporations and publicly held companies that own 10 % or more of stock in the party: eResearchTechnology, Inc. is wholly owned by Nordic Capital, a privately held company. No publicly held company owns 10 percent or more of the stock of eResearchTechnology, Inc.

The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are: Grace J. Pak of Wilson Sonsini Goodrich & Rosati; James M. Singer, William L. Stang, and Richard L. Holzworth of Fox Rothschild.

September 6, 2016

/s/ Edward G. Poplawski
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STATEMENT OF RELATED CASES

In accordance with Federal Circuit Rule 47.5, Appellant eResearchTechnology, Inc. ("ERT"), states that (1) there are not, and have not been, any other appeals in this civil action before this or any other appellate court; and (2) there are not any cases known to its counsel to be pending in this or any other court that will directly affect, or be directly affected by, this Court's decision in the pending appeal.

JURISDICTIONAL STATEMENT

The District Court had jurisdiction under 28 U.S.C. §§ 1331 and 1338, and entered dismissal for failure to state a claim on May 10, 2016. Appx1. ERT timely filed its notice of appeal on June 8, 2016. Appx115-116. This Court has jurisdiction under 28 U.S.C. § 1295.

STATEMENT OF THE ISSUES

Whether the District Court erred in granting Appellee CRF, Inc.'s ("CRF") motion to dismiss this action for failure to state a claim for relief on the basis that every claim in ERT's five asserted patents for clinical drug trials lacks patent eligibility under 35 U.S.C. § 101.

STATEMENT OF THE CASE

ERT is a leading provider of cloud platform solutions for clinical drug trials, including products and services that improve the accuracy and reliability of patient data associated with such trials. Appx3; Appx193-194; Appx376. ERT and CRF provide mobile technology for improving the research protocol compliance of patients participating in a clinical drug trial. Appx3; Appx193-194. Patient non-compliance substantially increases drug approval cost and the time required to approve a drug. *E.g.*, Appx40, '180 patent[1] at 1:23-2:3. ERT's five asserted software patents improve patient compliance by providing specific ways to determine, evaluate, predict and correct patient non-compliance. Appx40, '180 patent at 1:23-2:3; Appx96, '970 patent at 1:21-53; Appx63, '519 patent at 1:19-2:6; Appx82, '605 patent at 1:21-2:9; Appx107, '447 patent at 1:20-2:37. ERT filed this action against CRF in July 2015 averring that CRF's mobile technology, including its eCOA products, infringe ERT's three patents. Appx117-126. ERT filed an Amended Complaint in October 2015 adding two patents. Appx193-208. The District Court acknowledged that "both parties have a strong incentive to police their intellectual property assets" and that electronic systems can

[1] The asserted patents are U.S. Patent Nos. 8,065,180 (the '180 patent); 8,145,519 (the '519 patent); 8,433,605 (the '605 patent); 6,879,970 (the '970 patent); and 7,415,447 (the '447 patent).

substantially decrease costs and improve the quality of the clinical drug trial process. Appx3.

In lieu of responding to the Amended Complaint, CRF moved to dismiss this action for failure to state a claim under FED. R. CIV. P. 12(b)(6) on the ground that every claim in ERT's five asserted patents lacks patent eligibility under 35 U.S.C. § 101. On January 29 and March 10, 2016, the District Court heard oral argument on CRF's motion and granted it on May 10, 2016. Appx520-570; Appx571-634; Appx1.

STATEMENT OF THE FACTS

Clinical drug trials, which include human testing, are essential to assessing whether a proposed drug is safe and efficacious enough for human use to get regulatory approval. Appx40, '180 patent at 1:23-2:3; Appx403-466. Humans participating in clinical trials must comply with protocols to ensure that the data generated and analyzed has the requisite quality and integrity. Appx40, '180 patent at 1:23-48; Appx96, '970 patent at 1:20-45. These protocols address proper data entry and collection and completion of other assigned tasks by participating patients. Appx40, '180 patent at 1:51-2:3; Appx63, '519 patent at 1:55-2:6; Appx82, '605 patent at 1:58-2:9; Appx96, '970 patent, 1:34-53; Appx107, '447 patent at 2:6-37. Patient compliance rate is not only critical to generating valid, accurate and reliable data and analyzing it, but also to controlling, if not reducing,

the tremendous cost and time consumed in clinical trials. *Id*. Indeed, the District Court so acknowledged. Appx3.

Yet, patient non-compliance in clinical drug trials has been a significant risk and cost to the pharmaceutical industry. Appx40, '180 patent at 1:51-2:3; Appx63, '519 patent at 1:55-2:6; Appx82, '605 patent at 1:58-2:9; Appx96, '970 patent at 1:34-53; Appx107, '447 patent at 2:6-37. This non-compliance does not merely stem from erroneous patient data entry or inadequate data collection, but from fundamental problems that are unique to creating and carrying out research protocols in clinical trials. *Id*. These problems include the domain of the clinical trials, characteristics of the subjects, the propriety of the datasets, researcher bias, the errors inherent in the typical practice of evaluating compliance by examining only one variable at a time, and the inability of existing approaches to determine, evaluate, and predict compliance or lack thereof until serious noncompliance has already occurred. Appx40, '180 patent at 1:40-50-2:3; Appx63, '519 patent at 1:43-51; Appx82, '605 patent at 1:46-55; Appx96, '970 patent at 1:20-32; Appx107, '447 patent at 1:20-57. Replacement of paper diaries with electronic patient data collecting systems may mitigate one source of patient non-compliance (*i.e.*, improper physical data entry and collection) but does not adequately address fundamental considerations that affect patent compliance. *Id*. Thus, there has been a substantial need for a method and system to adequately identify, track, evaluate,

predict, manage and enhance patient research protocol compliance in clinical trials and thereby correct non-compliance, reduce clinical trial costs and completion time, and ultimately get a drug or medical device to market quicker. *Id*.

I. The '180 Patent

The '180 patent, entitled "Systems for Clinical Trial Subject Compliance," was filed on April 2, 2001 and issued on November 22, 2011. Appx31. It incorporates by reference the application which issued as the '970 patent. Appx40 at 1:6-14. The '180 patent has 34 claims, eight of which are independent claims. Appx47-51. Claims 1, 4, and 11 are independent method claims, and claims 19, 21, 22, 23, and 24 are independent computer-readable medium claims. *Id*. The focus of the '180 patent is specific ways to solve a technologic problem unique to clinical drug trials; namely that of inaccurate, unreliable and invalid data and results due to inadequate research protocol compliance of patients who participate in the trials and insufficient underlying evaluation of patient compliance. Appx40 at 1:15-2:3. The '180 patented invention addresses this problem by acquiring specified compliance data, and generating and applying specified comparative algorithmic techniques in response to historical data and individual participant data so as to produce a dedicated compliance assessment. Appx40 at 1:24-2:3; Appx42 at 6:38-10:34; Appx46-47 at 13:57-15:25. This assessment enables clinical trial staff to take specified actions to enhance individual patient compliance. *Id*. The

invention thus provides a specific, unconventional way to improve the accuracy, reliability and validity of the technologic process associated with research protocols in clinical drug trials. *Id*.

This improvement in research protocol compliance goes well beyond mere use of a computer or electronic device as a tool to do quick, efficient collection or delivery of patient data during clinical drug trials. *Id*. The '180 patent invention allows for "creation of appropriate research protocol, management and enhancement of subject behavior and effective distribution for clinical trial data." Appx40 at 1:61-64. The resulting benefits include "reliable, valid data; increased statistical power, reduced clinical trial costs through smaller sample sizes; reduced time to complete the clinical trial; and, ultimately, reduced time to get a drug or medical device to market." *Id.* at 1:61-2:3. As discussed below, the claims recite various embodiments of the invention described in the '180 specification that set forth differing comparative algorithmic techniques and other distinct features. Appx40-51. Thus, the independent claims have distinctively different limitations in relation to one another. *Id.*

Claim 11, which is by no means representative of the claims, reads as follows:

> A method of determining if an action is needed regarding subject compliance during a current clinical trial, wherein said current clinical trial comprise a group of subjects participating in said current clinical trial, comprising the steps of:

providing data on timeliness of a data entry and historical subject compliance data from a previous clinical trial, wherein said historical subject compliance data comprises data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state;

generating an algorithm by quantitative analysis of said data on timeliness of a data entry and said historical subject compliance data;

translating said algorithm into a decision rule for use during said current clinical trial;

obtaining subject compliance information from a subject in said group of subjects participating in said current clinical trial; and

comparing said subject compliance information from said subject in said group of subjects participating in said current clinical trial to said decision rule on a portable electronic device or a computer to determine if said action is needed for said subject in said group of subjects participating in said current clinical trial, wherein said action comprises removing all or part of data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial from said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial regarding compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on

> compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in monitoring and correcting of subject compliance.

Appx48.

Independent claims 1, 4 and 11 recite a **method** of "determining if action is needed regarding subject compliance" (claim 1) or "prompting an action if subject noncompliance indicates (claims 4 and 11) that includes (**1**) **providing** specific historical subject compliance data and specific information on data timeliness from a previous clinical trial, but which is not a patient's current data entry (claims 1, 4 and 11); (**2**) for use during the current clinical trial, **generating** a specified "predictive algorithm" that is "translated" into "at least one prediction rule" (claim 4) or a specified algorithm that is "translated" into a "decision rule" (claim 11), or a "preferred compliance threshold" by a specified quantitative analysis (claim 1); (**3**) **obtaining** subject compliance information on a **portable electronic device**[2] from a patient currently participating in the clinical trial (claim 1, 4, 11 and dependent claim 17); and (**4**) **comparing** such compliance information to the specified compliance threshold (claim 1), prediction rule (claim 4) or decision rule (claim 11) and **thereby determining** if specified action set forth in the claims is needed to be prompted for patient compliance. Appx47-48. This action includes

[2] Claim 11 does not expressly recite a portable electronic device but claim 17, which depends from claim 11, does so. Appx48.

correcting individual patient noncompliance, removing individual patient data, or removing a patient from the clinical trial. *Id*.

The District Court adopted ERT's proposed construction of "decision rule" to mean "reformatted algorithm." Appx11 at n.6. ERT supplied this construction in light of the '180 specification which states that "decision rules are basically reformatted algorithms that can be applied to current subject compliance data to determine whether action is needed." Appx46 at 14:30-33. Further, the '180 specification states that the '970 specification, which the '180 patent incorporates by reference, provides "additional details regarding such algorithms and decision rules. Appx43 at 7:54-59. The '970 specification sets forth an exemplary equation as a "sample decision rule" derived according to specified variables. Appx99 at 7:7-33.

Independent claims 19, 21, 22, 23 and 24 recite a "**computer readable medium**" suitable for use in an electronic device which has recorded instructions comprising steps similar to steps in companion method claims, including steps having a particular **comparative algorithmic technique** (*i.e.*, compare claims 1 and 19, 4 and 23, 11 and 24). Appx48-50. Claim 22 recites an additional comparative algorithmic technique that includes generating a specified **spectrum of compliance** and comparing individual patient compliance information to such spectrum. Appx49-50. In sum, when read as a whole, each '180 claimed

invention recites a specific way to collect current individual patient data, provide historical compliance data and, upon analyzing such data, then generate and apply specified comparative algorithmic techniques to individual patient data in order to determine what, if any, specific action is needed for individual patient compliance.

The ’180 patent specification provides additional contextual support for the claim language read as a whole, and in particular for focus on differing comparative algorithmic and compliance threshold techniques that enable specific actions to enhance individual patient compliance. There is not any indication in the specification that such techniques alone, or in combination with other claims requirements, were well-known, routine or conventional at the time of the inventions. Specifically, various embodiments describe generating, and applying through comparison with current individual compliance data, “empirically derived sets of algorithms and rules to predict, track and enhance subject compliance with research protocols” in which “a portable device is used to query and collect data from the subject.” Appx42 at 5:13-25; *see also* Appx36 at Fig. 2; Appx39 at Fig. 5; Appx43 at 7:42-67; Appx44 at 9:25-46, 10:35-45; Appx46 at 13:58-67, 14:28-47, 14:61-67. The specification emphasizes that “these empirically derived algorithms and rules allow the disclosed invention to examine the data for nonintuitive and complex combinations of predictors to proactively determine [compliance.]” Appx43 at 7:49-54. As set forth above, the ’180 and ’970

specifications have additional details regarding such algorithms and decision rules. *Id.* at 7:54-59. The specification further states that decision rules "may determine a threshold of compliance or a threshold of noncompliance," or "optionally a decision rule may identify a spectrum of noncompliance. Appx46 at 14:34-36. A companion approach in another embodiment involves generation of a preferred compliance threshold and comparing it with current individual patient data. Appx38 at Fig. 4; Appx40 at 2:14-21; Appx46 at 13:49-56.

For example, in the Fig. 5 embodiment, when a patient's current compliance data and specified historical compliance data from a prior clinical trial are provided, quantitative analysis is done to generate one or more algorithms. Such algorithm(s) are then "translated" into "specific decision rules" for assessing patient compliance, including "predict[ing] which patients will fail to complete a clinical trial protocol." Appx39 at Fig. 5; Appx46-47 at 13:49-15:10. Then, the "derived" decision rules, which are essentially "reformatted algorithms," are applied (*i.e.*, "compared") to individual patient compliance information to determine what, if any, specific action needs to be taken as to such individual patient. *Id.*

II. The '519 and '605 Patents

The '605 patent is a continuation of the '519 patent which is a continuation of the '180 patent. Appx72; Appx54. Like the '180 patent, both patents

incorporates by reference the application which issued as the '970 patent. Appx63, '605 patent at 1:6-16; Appx63, '605 patent at 1:6-18. Each patent addresses the same technologic problem unique to clinical drug trials as the '180 patent addresses, but focuses on further specific techniques to classify clinical trial results of a particular patient and thereby improve patient compliance. Similarly, there is no indication in the specification that these techniques were well-known, routine or conventional as of the time of the invention(s). Like the '180 patent (Appx40 at 1:23-2:3), the '519 and '605 patent specifications make clear that the fundamental problems addressed by the claimed inventions go well beyond data entry and collection in a paper diary or general electronic device. Appx63, '519 patent at 1:19-2:6; Appx82, '605 patent at 1:21-2:9.

Rather, the problems addressed include errors inherent in the typical practice of evaluating compliance by looking at one variable at a time and other flawed data evaluation approaches. *Id*. The '519 and '605 inventions enhance patient compliance through a specific technique that creates "one or more evaluability data categories" corresponding to an individual participant evaluability data and comparing certain categorized data to a "norm" so as to classify the clinical trial results for the individual participant. Appx63, Appx68, Appx69, '519 patent at 2:7-17, 11:50-12:38, 13:34-44; Appx82, Appx87, Appx88, '605 patent at 2:10-19,

11:63-12:60, 13:38-48. As set forth below, the '605 patent claims also add an additional specific analysis step.

The '519 Patent: There are 63 claims in the '519 patent, three of which are independent claims. Appx70-71 at 15:35-18:47. Claim 1 is an independent method claim; claim 22 is an independent computer readable medium claim; and claim 43 is an independent system claim. *Id.*

As an example, claim 1 states:

> A method for classifying clinical trial results from one or more participants in a clinical trial, the method comprising:
>
> > a. entering evaluability data from the one or more participants on an electronic device, wherein the evaluability data comprise one or more ***evaluability data categories***; and
> >
> > b. comparing the evaluability data from the one or more ***evaluability data categories*** to a norm to ***classify the clinical trial results*** from the one or more participants in the clinical trial based on a type of compliance, wherein the ***classifying allows analysis of participants with a similar type of compliance***.

Appx70 at 15:38-49 (emphasis added).

As shown above, claim 1 of the '519 patent provides a specific way to classify clinical trial results. It requires the use of evaluability data, which comprises "evaluability data categories." It further requires comparing the evaluability data from the evaluability categories to a norm to classify the clinical trial results based on a type of compliance. This would result in allowing analysis

of participants with a similar type of compliance. The '519 specification defines "evaluability data." Appx65 at 5:48-55. In light of the specification, ERT proposed a construction for "evaluability data categories" as follows: "categories of data that relate to circumstances under which trial data was collected or other data pertaining to characteristics of the trial data or other evaluability data."[3] *Id*.

The dependent claims of the '519 patent further require specific and concrete limitations. Appx70-71. For example, claim 5 requires "wherein the quantitative analysis comprises a statistical or data mining technique" (Appx70 at 15:59-60); claim 6 requires "wherein the statistical or data mining technique comprises logistic regression, discriminant function analysis, classification and regression trees, neural networks, or multiple linear regression" (*id.* at 15:61-64); claim 8 requires "wherein the another category comprises consistency with other collected data, proximity of the data to an expected data rage, and completeness of the data" (*id.* at 16:1-4); and claim 15 requires "wherein the evaluability database is a disease-specific database" (*id.* at 16:20-21).

The '605 Patent: There are 63 claims in the '605 patent, three of which are independent claims. Appx89-90. Claim 1 is an independent method claim; claim

[3] The District Court did not adopt this proposed construction or supply any construction. Appx9.

22 is an independent computer readable medium claim; and claim 43 is an independent system claim. *Id.*

As an example, claim 1 states:

> A method for classifying results from one or more participants in a clinical trial, the method comprising:
>
> a. electronically accessing evaluability data obtained during the clinical trial, wherein the evaluability data is from the one or more participants in the clinical trial, wherein the evaluability data is stored on an electronic device, wherein the evaluability data comprise data from one or more ***evaluability data categories***;
>
> b. comparing the evaluability data from the one or more ***evaluability data categories*** to a norm to ***classify clinical trial results*** from each of the one or more participants in the clinical trial based on a type of compliance; and
>
> c. analyzing the classified clinical trial results from the one or more participants with a similar type of compliance.

Appx89 at 15:40-54 (emphasis added).

The '605 specification defines "evaluability data." Appx84 at 5:49-55. ERT proposed a construction for "evaluability data categories" identical to that proposed for the same term in the '519 patent. Similar to the '519 patent, claim 1 of the '605 patent provides a specific concrete way to classify clinical results. It requires the use of evaluability data, which comprises evaluability data categories. It further requires comparing the evaluability data from the evaluability categories to a norm to classify the clinical trial results based on a type of compliance and

analyzing the classified clinical results from participants with a similar type of compliance.

The dependent claims of the ’605 patent further provide specific and concrete limitations. For example, claim 5 requires “wherein the quantitative analysis comprises a statistical or data mining technique” (Appx89 at 15:64-65); claim 6 requires “wherein the statistical or data mining technique comprises logistic regression, discriminant function analysis, classification and regression trees, neutral networks, or multiple linear regression” (*id.* at 15:66-16:2); claim 8 requires “wherein the another category comprises consistency with other collected data, proximity of the data to an expected data range, or completeness of the data” (*id.* at 16:6-9); and claim 15 requires “wherein the evaluability database is a disease-specific database” (*id.* at 16:24-25).

III. The ’970 and ’447 Patents

The ’970 and ’447 patents, each of which is entitled “Apparatus and Method for Prediction and Management of [Subject/Participant] Compliance in Clinical Research,” issued on April 12, 2005 and August 19, 2008 respectively. Appx91; Appx103. Both patents incorporate by reference the application which issued as the ’180 patent. Appx96, ’970 patent at 1:6-11; Appx107, ’447 patent at 1:8-16. The ’447 patent is a continuation-in-part of an application that is a continuation of the April 2, 2001 application that led to the ’970 patent. Appx107 at 1:8-16. Each

invention "relates to the prediction of [subject participant] compliance with protocols" in clinical drug trials. Appx96, '970 patent at 1:15-18; Appx107, '447 patent at 1:20-25. Like the '180, '519 and '605 patents, the focus of the '970 and '447 patents is to solve a technologic problem unique to clinical drug trials; namely that of inaccurate, unreliable and invalid data and results due to inadequate research protocol compliance of patients who participate in the trials and insufficient underlying evaluation of subject compliance. Appx96, '970 patent at 1:21-46; Appx107, '447 patent at 1:27-57; 2:6-22. Each patent stresses that "predicting subject performance and assessment of such performance is of substantial value to clinical research" in light of the significant risk and cost to the pharmaceutical industry from noncompliance. Appx96, '970 patent at 1:41-46; Appx107, '447 patent at 2:17-22.

The '447 and '970 patents specifically relate to comparative and other specified algorithmic techniques that predict individual participant/subject compliance with research protocols so as to enhance individual compliance Appx96, '970 patent at 1:15-18, 1:42-67; Appx107, '447 patent at 1:20-25; 2:19-47. Thus, each invention provides a specific, unconventional way to improve the accuracy, reliability and validity of the technologic process associated with research protocols in clinical drug trials. Appx96, '970 patent at 1:21-2:33; Appx107, '447 patent at 1:27-2:37. This is specific and concrete application that

solves a problem unique to clinical drug trials. This improvement in research protocol compliance goes well beyond mere use of a computer to do quick, efficient collection or delivery of patient data during clinical drug trials. *Id*. The benefits of implementing the patented inventions include "reliable, valid data; increased statistical power; reduced clinical trial costs through smaller sample sizes; reduced time to complete the clinical trial; and, ultimately, reduced time to get a drug or medical device to market." Appx96, '970 patent at 1:45-52; Appx107, '447 patent at 2:23-37. There is no indication in the specification that any of these techniques of predicting patient compliance were well-known, routine or conventional as of the time of the invention(s).

As discussed below, the claims recite various embodiments of the '970 and '447 inventions which are described in the '970 and '447 specifications respectively and set forth differing algorithmic techniques and other distinct features. Appx96-102, 107-114. Thus, the independent claims, and related dependent claims, have distinctively different limitations in relation to one another. *Id.*

The '970 Patent: There are 37 claims in the '970 patent, ten of which are independent claims as follows: (1) method claims 1, 9, 14, 17, and 18; and (2) medium claims 25, 29, 33, 36, and 37. Appx100-102.

The independent method claims recite a method of predicting/determining subject compliance (claims 1, 9 and 14) or fraud (claims 17 and 18) that includes **(1) providing** historical subject compliance data, **(2) providing** historical protocol data (only claims 9, 14 and 17), **(3) generating** a specified predictive algorithm (claim 1) or a specified reflective algorithm (claim 9) or a specified spectrum of compliance (claim 14) or a specified "fraud detection algorithm" (claims 17 and 18), **(4) translating** the predictive/reflective/fraud algorithm into a "decision/fraud detection rule" (claims 1, 9, 17 and 18), and for independent claims 9, and 14 **(5a) obtaining** the subject compliance information,[4] and **(5b) comparing** such compliance information to the decision rule (claim 9) or spectrum of compliance (claim 14) or the fraud detection rule (claim 19 dependent from claim 18) and thereby predicting/determining subject compliance or detecting fraud in compliance. Appx100-101.

Various dependent method and medium claims add implementation of a portable electronic device (claims 4, 11, 16, and 21). Appx100-101. Like the '180 patent, the '970 patent describes "decision rule" "essentially reformatted algorithms that can be applied to current subject compliance to determine whether

[4] Dependent claims corresponding to the independent method claims 1, 9, 14, and 18 that obtaining and/or compliance determination is done with a portable electronic device (*e.g.*, claims 3-4, 10-11, 15-16 and 21). Appx100-101.

action is needed." Appx98 at 6:67-7:2. Hence, the same construction applies as ERT proposed for '180 patent.

The independent medium claims 25, 29, 33, 36, and 37 recite "a medium suitable for use in an electronic device" and which has "instructions for execution on the electronic device comprising steps similar to steps in companion method claims, including steps having particular algorithmic techniques (compare claims 1 and 25; 9 and 29; 33 and 14; 17 and 36; 18 and 37. Appx100-102. In sum, when read as a whole, the independent method and medium claims get historical and/or protocol data and/or individual patient data, generate specified algorithms or compliance spectra, translate generated algorithms and apply specified comparative algorithmic techniques to individual patient data to predict or determine compliance, including fraud detection.

Claim 1, which is by no means representative of the claims, states:

> A method of predicting subject noncompliance, comprising the steps of:
>
> providing historical subject compliance data;
>
> ***generating*** at least one ***predictive algorithm*** for predicting subject noncompliance by ***quantitative analysis*** of the historical subject compliance; and
>
> ***translating*** the at least one ***predictive algorithm*** into at least one ***prediction rule*** for use with a clinical trial.

Appx100 at 10:42-49 (emphasis added).

Claim 2, which depends from claim 1, states:

> The method of predicting subject noncompliance of claim 1, further comprising the steps of:
>
> obtaining subject compliance information; and
>
> comparing the subject compliance information to the at least one prediction rule to determine if action is needed.

Id. at 10:50-55.

The '970 patent specification, provides additional contextual support for the claim language read as a whole, and in particular the focus on techniques that involves generating a specified algorithm which is translated into specified decision rule that is then compared with compliance information so as to predict or detect the non-compliance of an individual, including fraud detection, during clinical drug trials. There is not any indication in the specification that such techniques alone, or in combination with other claims requirements, were well-known, routine or conventional at the time of the inventions. Specifically, various embodiments describe translating specified algorithms into decision rules which are then compared with individual compliance data so as to predict non-compliance, including fraud. *See, e.g.*, Appx98-99 at 6:64-8:54. The specification defines decision rules as "essentially reformatted algorithms that can be applied to current subject compliance to determine whether action is needed." *Id*. at 6:67-7:2.

The specification provides as illustrative equation for a decision rule derived according to specified variables. Appx99 at 7:7-27.

As shown above, claim 1 provides a specific and concrete way to predict subject noncompliance in a clinical trial. It requires providing specific data, *i.e.*, historical subject compliance data; generating a predictive algorithm by quantitative analysis of the historical subject compliance; and translating the predictive algorithm into a prediction rule. Claim 1 is by no means a representative claim of the '970 patent. For example, other independent claims require further limitations such as "obtaining the subject compliance information" and "comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed." Appx101-102 at claims 9, 14, 29, 33. The dependent claims further add various concrete and specific limitations not found in the independent claims. Appx100-102 at 10:41-14:37. For example, as set forth above dependent claim 2 adds steps, including a specified comparative algorithmic technique related to predicting patient (a/k/a "subject") compliance.

The '447 Patent: There are 30 claims in the '447 patent. Appx114. The three independent claims (*i.e.*, 1, 16 and 23) recite a particular computer implemented method that provides a specific and concrete way to determine clinical trial participant compliance (claim 1), or identify a suitable clinical trial site for conducting a clinical trial (claim 16) or predict success of a clinical trial

involving a selected clinical trial participant (claim 23). *Id.* No one of these claims is representative of the others.

Claim 1 implements a specified algorithmic technique which includes **(1) providing** specific data, *i.e.*, historical participant compliance data, **(2) generating** an algorithm for determining participant noncompliance by quantitative analysis, **(3) applying** the algorithm to determine participant compliance, and **(4) outputting** notice of noncompliance. *Id.* Dependent claim 2 adds the step of **translating** the algorithm into at least one **decision rule** for with a clinical trial. *Id.* Like the '180 and '970 patents, the '447 patent describes "decision rule" "essentially reformatted algorithms that can be applied to current subject compliance to determine whether action is needed." Appx111 at 10:13-16. Hence, the same construction applies as ERT proposed for '180 patent.

Claims 16 requires a different set of limitations than claim 1: "providing a database storing historical compliance data for a plurality of clinical trial sites," "performing a statistical analysis of the historical compliance data for each clinical trial site to predict compliance in a future clinical trial," and "selecting a clinical trial site that is predicted to comply with research protocols." Appx114. Claim 23 is also different. It is directed to predicting success of a clinical trial involving a selected clinical trial participant. Claim 23 requires "providing historical compliance data from a clinical trial involving the clinical trial participant,"

"performing a quantitative analysis of the data to identify whether the participant is likely to produce data in compliance with research protocol in the future," and "identifying whether the participant is likely to produce data in compliance with research protocols in the future." *Id.*

As an example, claim 1 states:

> A computer implemented method of determining noncompliance of a participant in a clinical trial, comprising the steps of:
>
> providing historical participant compliance data;
>
> ***generating*** at least one ***algorithm*** for determining participant noncompliance by ***quantitative analysis*** of the historical participant compliance data;
>
> applying the at least one algorithm to determine participant compliance; and
>
> ***outputting*** notice of noncompliance.

Appx114 at 15:4-13 (emphasis added).

Dependent claim 2 states:

> The method of claim 1, further comprising the step of translating the at least one algorithm into at least one decision rule for use with a clinical trial.

Id. at 15:14-16.

As shown above, claim 1 provides a specific and concrete way to determine non-compliance of a participant in a clinical trial. It requires providing specific data, *i.e.*, historical participant compliance data; generating an algorithm for determining participant noncompliance by quantitative analysis; applying the

algorithm to determine participant compliance; and outputting notice of noncompliance. Claim 1 is by no means a representative claim of the '447 patent. For example, claim 16 is directed to a specific and concrete way to identify a suitable clinical trial site for conducting a clinical trial. It requires a different set of limitations than claim 1: "providing a database storing historical compliance data for a plurality of clinical trial sites," "performing a statistical analysis of the historical compliance data for each clinical trial site to predict compliance in a future clinical trial," and "selecting a clinical trial site that is predicted to comply with research protocols." Appx114 at 16:4-13. Claim 23 is also different. It is directed to predicting success of a clinical trial involving a selected clinical trial participant. Claim 23 requires "providing historical compliance data from a clinical trial involving the clinical trial participant," "performing a quantitative analysis of the data to identify whether the participant is likely to produce data in compliance with research protocol in the future," and "identifying whether the participant is likely to produce data in compliance with research protocols in the future." *Id.* at 16:34-43. Similarly to the '970 specification, the '447 specification provides additional contextual support for the foregoing reading of the claim language as a whole. Appx111-112 at 10:11-11:63.

SUMMARY OF THE ARGUMENT

ERT has a family of five patents that improve patient compliance with research protocols used in clinical drug trials. The claimed inventions in each of these patents provide various specific, unconventional ways to do so, including through comparative and other algorithmic techniques that enhance compliance and correct non-compliance. In contrast, the intrinsic record reflects that neither use of paper diaries nor mere replacement of such diaries with electronic data collection systems adequately addresses patient non-compliance. The District Court erred in dismissing this action for failure to state a claim for relief on the basis that every claim in ERT's five asserted patents lacks patent eligibility under 35 U.S.C. § 101. Accordingly, the District Court's order should be reversed and the action should be remanded so that it can proceed.

The District Court committed four fundamental errors that ramify throughout its patent eligibility assessment of every claim in ERT's five asserted patents: (1) failure to accept as true and credit the evidence in the intrinsic record while wrongly substituting in its place extraneous "evidence" of activities found patent ineligible in prior cases(s); (2) identifying a single claim in each patent as representative and not crediting ERT's proposed claim constructions and the differing limitations among the independent and dependent claims; (3) concluding that under the *Alice/Mayo* § 101 two-step test the claims are "directed to" an

abstract idea (*i.e.*, step one); and (4) alternatively lack sufficient inventive concept or transformative nature for patent eligibility (*i.e.*, step two).

I. The '180 Patent

The '180 patent has eight independent claims which, among other things, focus on *differing* comparative algorithmic and compliance threshold techniques that determine what, if any, specific action, is appropriate to enhance individual patient compliance with research protocols. For example, independent claims 11 and 24 involve generating a specified algorithm that is "translated" into a "decision rule" followed by comparison of the decision rule to individual patient compliance information to determine what, if any, specific action needs to be taken as to such individual patient.

First, the District Court erroneously treated claim 1 as representative of all '180 claims, despite acknowledging the differing algorithmic techniques.

Second, neither claim 1 nor any of the other '180 claims is directed to an abstract idea (*i.e.*, *Alice/Mayo* step one). When properly tethered to the claim language and viewed in light of the specification, the focus of each claim is a specific way to solve a technologic problem unique to clinical trials with specified algorithmic techniques that differ among the various independent claims. Yet, the District Court wrongly equated the "heart" of the invention with the abstract idea of replacing paper diaries with a general electronic device as a mere tool for data

collection and analysis. The District Court's characterization of the claims at such a high level of abstraction ignored the intrinsic evidence that the claimed specific way is not well-known, routine, or conventional in the clinical drug trial industry, or even a fundamental economic practice. Indeed, CRF invited this error at oral argument, along with inviting the District Court to conflate Section 112 and Section 101.[5] The District Court also did not credit the differing claim limitations, including ERT's construction for decision rule as a "reformatted algorithm." Ultimately, the District Court misapplied the Rule 12(b)(6) standard by impermissibly substituted extraneous fact finding for the intrinsic record that directly contradicted its finding.

Third and alternatively, the '180 claims are patent eligible because they have sufficient inventive concept and requirements that transform the nature of the claims into patent eligible subject matter (*i.e.*, *Alice/Mayo* step two). In particular, when viewed as an ordered combination and in light of the specification, the claim limitations provide a specific technologic solution embodying differing algorithmic techniques that address a specific technologic problem unique to clinical drug trials. As such, they do not preempt every application of conducting clinical trials. Further, the '180 intrinsic record confirms that this inventive concept is not

[5] CRF's invitation also ostensibly tainted all of the District Court's patent eligibility determinations.

routine, generic, or conventional. Finally, by their very nature the claims require transforming original compliance data into new or different data, thereby fundamentally altering the original data into other different data.

II. The '519 and '605 Patents

The '519 and '605 patents address the same technologic problem unique to clinical drug trials as the '180 patent addresses, but focus on further specific techniques to classify clinical trial results of a particular patient and thereby improve patient compliance. Like the '180 patent, the '519 and '605 patent specifications make clear that the claimed inventions go well beyond data entry and collection in a paper diary or general electronic device. The District Court identified method claim 1 of the '519 patent as representative of all '519 ***and*** '605 claims and found the '605 claims to be patent ineligible for the same reasons as the '519 claims.

First, none of the '519 or '605 claims is directed to an abstract idea (*i.e.*, *Alice/Mayo* step one). The District Court erred by failing to credit ERT's proposed construction for "evaluability data categories" and describing the claims at an unduly high level of abstraction which it wrongly equated with the conventional practice similar to that described in another district court decision (*i.e.*, *Erie*). The District Court's finding was contrary to the Rule 12(b)(6) standard, since the

intrinsic evidence showed that the specific claimed way was not well-known, routine or conventional as of the time of the invention.

Second and alternatively, when properly construed and considered as an ordered combination in view of the specification, the ’519 and ’605 claim limitations do not attempt to preempt every application in the field, but provide a specific, unconventional solution to a unique problem in the field (*i.e.*, *Alice/Mayo* step two). Thus, the claims are patent eligible because they have sufficient inventive concept.

III. The ’970 and ’447 Patents

The ’970 and ’447 patents specifically relate to comparative and other specified algorithmic techniques that predict individual participant/subject compliance with research protocols so as to enhance individual compliance. There is no indication in the specification that any of these techniques of predicting patient compliance were well-known, routine or conventional as of the time of the invention(s).

First, the District Court erroneously treated each claim 1 in the ’970 and ’447 patent as representative of all ’970 and ’447 claims, despite the differing algorithmic techniques.

Second, none of the ’970 or ’447 claims is directed to an abstract idea (*i.e.*, *Alice/Mayo* step one). When properly tethered to the claim language and viewed

in light of the specification, the focus of each claim is a specific way to solve a technologic problem unique to clinical trials with specified algorithmic techniques that enhance individual compliance through predicting individual participant compliance. The District Court erred in describing the claims at a high level of abstraction which it wrongly equated with routine and conventional economic practice per *OIP*, *CyberSource* and *Ultramercial*. The District Court also failed to credit the differing limitations in the claims, including ERT's construction of decision rule in various claims, and misapplied the Rule 12(b)(6) standard.

Third and alternatively, the '970 and '447 claims are patent eligible because they have sufficient inventive concept and requirements that transform the nature of the claims into patent eligible subject matter (*i.e.*, *Alice/Mayo* step two). In particular, the claim limitations as an ordered combination, when viewed in light of the specification, require transforming original compliance data into new into new or different data, thereby fundamentally altering the original data into other different data. Further, the claims of the '970 and '447 patents provide inventive concepts—which are specific and concrete—for resolving a particular problem in clinical trials and thus do not preempt every application of conducting clinical trials.

ARGUMENT

I. Standard of Review and Legal Framework

A. Motion to Dismiss

This Court reviews a district court's dismissal for failure to state a claim under the law of the regional circuit. *Bascom Global Internet Servs. v. AT&T Mobility, LLC,* No. 2015-1763, 2016 U.S. App. LEXIS 11687, at *13 (Fed. Cir. June 27, 2016). The Third Circuit applies a *de novo* standard of review for a dismissal under FED. R. CIV. P. 12(b)(6). *Phillips v. County of Allegheny*, 515 F.3d 224, 229 (3d Cir. 2008). Thus, a reviewing court is to accept all factual allegations as true, construe those truths in the light most favorable to the plaintiff, and then draw all reasonable inferences from them. *Connelly v. Lane Const. Corp.*, 809 F.3d 780, 790 (3d Cir. 2016). Similarly, a patent's claims are to be "construed in favor of the nonmovant." *Bascom*, 2016 U.S. App. LEXIS 11678 at *21. Conversely, it is improper to consider extrinsic evidence outside of the complaint or make extraneous fact finding outside the record. *TLI Communs. LLC v. AV Auto., L.L.C.*, 823 F.3d 607, 613-14 (Fed. Cir. 2016) (Section 101 dismissal motion); *Schmidt v. Skolas*, 770 F.3d 241, 249 (3d Cir. 2014) (a court should only consider the allegations and exhibits in the complaint, documents "integral to or explicitly relied upon" it, and matters of public record). Indeed, at this stage, a court cannot make fact findings at all. *Id*. This Court also reviews *de novo* a

district court's determination of patent eligibility under 35 U.S.C. §101. *Bascom*, 2016 U.S. App. LEXIS 11678 at *12. While ultimately a legal conclusion, Section 101 may contain underlying factual issues. *Accenture Global Servs., GmbH v. Guidewire Software, Inc.*, 728 F.3d 1336, 1340 (Fed. Cir. 2013).

B. The Legal Framework for Patent Eligibility

1. The Two Step Test

Under 35 U.S.C. § 101, patent eligible subject matter includes "any new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof." The judicially recognized exceptions to patent eligibility are "[l]aws of nature, natural phenomena and abstract ideas." *Alice Corp. Pty. Ltd v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014). Preemption is "the concern that drives this exclusionary principle. *Id*. That is, "the concern that patent law not inhibit further discovery by improperly tying up the future use of these building blocks of humanity." *Id*. (quoting *Mayo Collaborative Services v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1301 (2012)); *see also Rapid Litig. Mgmt. v. CelllzDirect, Inc.*, No. 2015-1570, 2016 U.S. App. LEXIS 12352, at *21-22 (Fed. Cir. July 5, 2016) (acknowledging that, while preemption is "not the test for determining patent-eligibility, it is certainly 'the concern that undergirds'" eligibility) (internal citation omitted). However, courts "must tread carefully in

construing this exclusionary principle lest it swallow all of patent law." *Alice*, 134 S. Ct. at 2354.

In *Mayo*, the Supreme Court set forth, and later reaffirmed in *Alice*, a two-step analytical framework for determining patent eligibility. *Mayo*, 132 S. Ct. at 1296-97 (law of nature); *Alice*, 134 S. Ct. at 2355 (abstract idea); *see also Bascom*, 2016 U.S. App. LEXIS 11687 at *12 (abstract idea); *Enfish, LLC v. Microsoft Corp*, 822 F.3d 1327, 1333-34 (Fed. Cir. 2016) (abstract idea). Specifically, first a Court must "determine whether the claims at issue are directed to one of those patent-ineligible concepts." *Alice*, 134 S. Ct. at 2355. "If not, the claims pass muster under § 101." *Ultramercial, Inc. v. Hulu*, 772 F.3d 709, 714 (Fed. Cir. 2014). If yes, as a second step, the court asks "[w]hat else is there in the claims before us?" *Id*. That is, the court in the second step is to "consider the elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application. *Id*. (quoting *Mayo*, 132 S. Ct. at 1297). *Alice* also states that the Supreme Court has "described step two of this analysis as a search for an "'inventive concept'"—*i.e.*, an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself." *Id*. (quoting *Mayo*, 132 S. Ct. at 1294).

This Court has described the first step as "looking at the 'focus' of the claims, their 'character as a whole.'" *Elec. Power Group, LLC v. Alstom S.A.*, No. 2015-1778, 2016 U.S. App. LEXIS 13861, at *5 (Fed. Cir. Aug. 1, 2016); *Enfish*, 822 F.3d at 1335. Thus, the "directed to" inquiry "cannot simply ask whether the claims *involve* a patent-ineligible concept, because essentially every routinely patent-eligible claim" involves laws of nature, natural phenomena and abstract idea. *Enfish*, 822 F.3d at 1335. Instead, the "directed to" inquiry "applies a stage-one filter to claims, considered in light of the specification, based on whether 'their character as a whole is directed to excluded subject matter.'" *Id.* For the abstract idea exception, it is appropriate to ask whether the focus of the claims is on a specific way or implementation or improvement that addresses a particular problem beyond just applying conventional or routine concepts or using a general purpose computer. *See id.*; *Diamond v. Diehr*, 450 U.S. 175, 184, 187 (1981) ("That respondents' claims involve the transformation of an article, in this case raw, uncured synthetic rubber, into a different state or thing cannot be disputed. The respondents' claims describe ***in detail*** a step-by-step method for accomplishing such, beginning with the loading of a mold with raw, uncured rubber and ending with the eventual opening of the press at the conclusion of the cure. . . . Our earlier opinions lend support to our present conclusion that a claim drawn to subject matter otherwise statutory does not become nonstatutory simply

because it uses a mathematical formula, computer program, or digital computer.") (emphasis added); *Alice*, 134 S. Ct. at 2358 (a claim to a computer implemented process for curing rubber using a well-known mathematic equation in a process designed to solve a technologic problem in the industry was patent eligible because it "improves an existing technologic process"); *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1257 (Fed. Cir. 2014) ("Instead, the claimed solution is necessarily rooted in computer technology in order to overcome a problem specifically arising in the realm of computer networks.").

This Court has further cautioned against overgeneralizing a claim's focus or describing the "claims at such a high level of abstraction and untethered from the language of the claims" which "all but ensures that exceptions to § 101 swallow the rule." *Enfish*, 822 F.3d at 1337. Nevertheless, this Court has observed that the relatedness between the two steps may involve "overlapping scrutiny of the content of the claims" and "close questions about when the inquiry should proceed from the first [step] to the second" such that at times a claim determined to be patent eligible under step two could also have be determined to be so under step one alone. *Elec. Power Group*, 2016 U.S. App. LEXIS 13861 at *6 (citing *TLI*, 823 F.3d at 611-15; *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1375 (Fed. Cir. 2016); *Enfish*, 822 F.3d at 1339; *Rapid Litig.*, 2016 U.S. App. LEXIS 12352 at *6-7; and *Bascom*, 2016 U.S. App. LEXIS 11687 at *5).

In applying step one, this Court has found it appropriate to look to whether prior precedent has classified certain fundamental economic activities as conventional or routine and thus patent ineligible as abstract ideas even when implemented on a computer. *Enfish*, 822 F.3d at 1333-34; *OIP Techs., Inc. v. Amazon.com, Inc.,* 788 F.3d 1359, 1362 (Fed. Cir. 2015). In this regard, "well-understood, routine, and conventional" activity means ***previously known*** activity or practice in the ***relevant industry***. *Alice*, 134 S. Ct. at 2358-59; *Bilski v. Kappos*, 130 S. Ct. 3218, 3230 (2010). To this end, certain prior precedent has classified certain financial and business activities or practices as such and this patent ineligible, including when implemented on a general purpose computer. *Id.* Again, however, for a Rule 12(b)(6) motion, it is not proper to classify activity as such in derogation of the intrinsic record. Nor is proper to make extraneous fact findings derived from prior classification of such activity in prior case law when the classification is incompatible with the intrinsic record (*e.g.*, the claims in light of the patent specification).

2. The Section 101 Inquiry is Separate and Distinct From Other Sections

The Section 101 "patent-eligibility inquiry is only a threshold test" and is distinct from other requirements for patent protection, such as §§ 102, 103 and 112. *Bilski*, 130 S. Ct. at 3224; *cf. Bascom*, 2016 U.S. App. LEXIS 11687 at *14 (§ 101 "is independent of—and on equal footing with—any other statutory

provision."). It is, therefore, improper to delve into § 102, 103 or 112 in assessing § 101 patent eligibility. *See Parker v. Flook*, 437 U.S. 584, 588 (1978) ("This case turns entirely on the proper construction of § 101 of the Patent Act, which describes the subject matter that is eligible for patent protection. It does not involve the familiar issues of novelty and obviousness that routinely arise under §§ 102 and 103."); *Diehr*, 450 U.S. at 191 ("In this case, it may later be determined that the respondents' process is not deserving of patent protection because it fails to satisfy the statutory conditions of novelty under § 102 or nonobviousness under § 103. A rejection on either of these grounds does not affect the determination that respondents' claims recited subject matter which was eligible for patent protection under § 101."); *Bascom*, 2016 U.S. App. LEXIS 11687 at *21 (observing that the district court's § 101 analysis "looks similar to an obviousness analysis under [§ 103] except lacking an explanation of a reason to combine the limitations as claimed.").

Vague or indefinite claim language is the province of § 112. *See Research Corp. Techs. v. Microsoft Corp.*, 627 F.3d 859, 869 (Fed. Cir. 2010). Moreover, § 101's "equal footing" dictates that the challenger should bear the burden of proving patent ineligible subject matter by clear and convincing evidence. *Cf. Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2242-43 (2010).

II. The '180 Patent Claims are Patent Eligible Subject Matter

A. The Claims are Directed to a Patent Eligible Concept Under Step One

For its patent eligibility assessment, the District Court identified method claim 1 of the '180 patent as representative of all '180 claims, albeit acknowledging that other independent claims recite different algorithmic techniques. Appx11. Then, it determined that claim 1 is directed to an abstract idea (Appx15), because the "heart" of the invention equates with using an electronic device in lieu of a "pen-and-paper diary for clinical trial data collection and analysis. Appx13. The District Court gave two bases for its determination. First, it characterized "the individual steps" of method claim 1 as "gathering data, analyzing same, and acting pursuant to that data," and concluded that such steps "are similar to others that have been found to be abstract" in two prior cases: *OIP*, 788 F.3d at 1361-62 and *Intellectual Ventures v. Erie Indem. Co*., No. 1:14-cv-00220, 2015 U.S. Dist. Lexis 129153, *55 (E.D. Pa. 2015). Appx13.[6] Second, the District Court indicated that limiting the invention to the particular technologic environment of clinical trials was not enough. Appx14. The Court declined to credit any of the specific algorithmic claim limitations ERT urged, despite

[6] This characterization constituted a higher level of abstraction than the District Court's generalized initial description of method claim 1 and did nothing to differentiate among algorithmic techniques in the claims. Appx10.

acknowledging the differing limitations in the eight independent claims and adopting ERT's proposed construction for "decision rule" in independent claims 11, 21, and 24. Appx10-11, Appx14; *see also* Appx608-609.

The District Court erred in classifying claim 1 as representative and describing the claims at an unduly high level of abstraction in which it wrongly equated the "heart" of the invention with the abstract idea of simply replacing conventional diary data collection and analysis with a general electronic device similar to the claims at issue in *OIP* and *Erie*. When tethered to the claim language and viewed in light of the specification, the ***focus*** of the claims is a ***specify way*** to solve a ***technologic problem unique to clinical trials*** with specified algorithmic techniques that differ among the various independent claims. Independent claims 11 and 24 (method and computer readable medium, respectively), for example, includes two key steps which focus on translating a specified generated algorithm" into "at least one decision rule" that is compared with specified compliance information on an individual participant so as to determine if specified action set forth in the claim is needed for patient compliance. Appx48; Appx50. Other independent claims have different comparative algorithmic techniques and as such are not "substantially similar" enough to claim 1 to be their representative. *See Content Extraction & Transmission LLC v. Wells Fargo Bank, N.A.*, 776 F.3d 1343, 1348 (Fed. Cir. 2104). The District Court's characterization of the claims at

a high level of abstraction ignored the specific differing claim limitations, including ERT's construction for decision rule.

The implementation of the patented claims delivers a dedicated compliance assessment for research protocols that improves the accuracy, reliability and validity of the clinical trial process on an individual participant basis and thereby reduces trial costs and duration and the time to get a drug to market. *See Alice*, 134 S. Ct. at 2358 (describing *Diehr* as holding that a computer implemented process using a well-known mathematical formula for curing rubber was patent eligible because it improved on an existing technologic process); *Stoneeagle Servs., Inc. v. Pay-Plus Solutions, Inc.,* No. 8:13-cv-2240-T-33MAP, 2015 U.S. Dist. LEXIS 85789, at *20 (M.D. Fla. July 1, 2015) (claims not abstract where "[t]he claims seek to address a problem uniquely within the health care industry" (*i.e.*, time and cost of generating and mailing physical checks) that goes beyond merely computerizing a routine business practice).

The focus of the claimed invention, therefore, does not equate with replacing paper diaries in clinical trials with a general electronic device as a mere tool to collect and analyze participant data. Indeed, the '180 patent specification makes clear that claimed invention goes well beyond such a mere substitution. *See* Appx40 at 1:24-2:3; Appx42 at 6:38-10:34; Appx46-47 at 13:57-15:25. That is, after describing the problems with use of paper diaries, the specification describes

other fundamental problems unique to research protocols and discloses various embodiments which address these problems with comparative algorithmic techniques. *See, e.g.*, *id.* There is no evidence in the specification or elsewhere in the record that the specific way of the claimed invention is well-known, routine, or conventional in the drug trial industry, or even that it is a fundamental economic or business practice. The District Court thus further erred by failing to accept as true on a dismissal motion the facts in the intrinsic record that directly contradicted its assessment. *See TLI*, 823 F.3d at 613-14 (extraneous fact finding outside the record is not permitted on Rule 12(b)(6) motion). ERT urged the District Court to read the claims as whole in light of the specification in order to ascertain whether the claimed invention was merely carrying out some well-known practice and indicated the absence of any evidence in the specification that claim limitations were routine or conventional. Appx604-606; Appx527-529, Appx544.

However, CRF invited error by improperly telling the District Court that it should disregard the fact that the '180 specification did not "put forth anything" that "is generic or routine," because a patent application drafter would never disclose what would be "a killer for the patent application." Appx628-629. CRF repeatedly also invited error by urging the Court to find patent eligibility because the '180 claims lack limitations, including the term decision rule, lack specificity.

Appx590, Appx597, Appx599. ERT explained that this approach erroneously conflated a § 112 with § 101. Appx605.

The District Court's reliance on *OIP* and *Erie* is misplaced. The claims in *OIP* were directed to "offer-based optimization" which was equated with "other 'fundamental economic concepts' found to be abstract by the Supreme Court and this Court." 788 F.3d at 1362.[7] Similarly, a district court in *Erie* determined that a method of collecting information was similar to "longstanding well-known methods of organizing human activity where the patent specification itself acknowledged the method implemented conventional discovery rules on a general computer." 2015 U.S. Dist. LEXIS 129153 at *94.

Finally, the District Court cited *NexusCard, Inc. v. Kroger Co*, No. 2:15-cv-968-JRG-RSP, 2016 U.S. Dist. LEXIS 38857, at *10-12 (E.D. Tex. Mar. 24, 2016) for the proposition that "patent claims with even more specific steps [than the '180 claims] have been found to be directed to abstract ideas." Appx14. However, *Nexus* is easily distinguishable, because the patentee acknowledged that the subject matter of the claimed invention was known, although not widely implemented. *Id*. The *Nexus* court rejected this argument on the ground that the "prevalence of an

[7] This Court also determined the claims in *OIP* lacked an inventive concept under step two, because they were merely directed to automation of a conventional method. 788 F.3d at 1361-62.

abstract idea does not factor into a patent-eligibility analysis." *Id*. Of course, *Erie* and *Nexus* are district court opinions and thus lack precedential value.

B. Alternatively, the '180 Claims are Patent Eligible Under Step Two

Using claim 1 as representative, the District Court determined that the '180 claims are not patent eligible under step two because they lack sufficient (1) "additional inventive features" or (2) transformative nature and (3) are not *DDR Holdings* type claims confined to an Internet environment. Appx15-19. The District Court erred.

Specifically, as to the first two reasons, the Court held that the claim limitations, alone and in combination "fail to transform the otherwise abstract ideas into patent eligible applications ***because they merely recite common, well-known steps***." Appx15 (emphasis added). For claim 1, the court found that the first and third limitations lack any "additional inventive steps" because they simply describe "routine data gathering techniques" like the steps in *OIP*; namely providing or obtaining data. Appx15-16. Next, the District Court collapsed the second and fourth limitations (*i.e.*, generating and comparing) into one limitation which it found "does not add inventiveness because it requires the ***application of conventional, well-known analytical steps***" like the claimed steps in *Ultramercial*, 772 F.3d at 716. Appx16 (emphasis added). The District Court also characterized the "computer-readable medium" claims as "simply applying otherwise abstract

claims" to a general computer and the additional steps in dependent claims 6, 26 and 28 as insufficiently transformative. Appx16-17. It also found that the underlying transformation in the claims was mere data reorganization or manipulation that did not add new or different data. Appx18. Lastly, the District Court found that *DDR Holdings* was "unavailing because the claims at issue do not address a problem unique to the Internet. *Id.*

The District Court carried over to its step two analysis its erroneous classification of claim 1 as representative, and its unduly abstract description of the claimed invention which failed to accept as true the factual evidence in the intrinsic record of a sufficient inventive concept and the invention's transformative nature. Here, particularly when viewed in ordered combination and in light of the specification, the claim limitations provide a specific technologic solution embodying differing comparative algorithmic techniques that address a specific technologic problem arising in research protocols in clinical drug trials. The intrinsic record within the '180 specification confirms that this inventive concept is not routine, generic or conventional. *See, e.g.*, Appx40 at 1:24-2:3; Appx42 at 6:38-10:34; Appx46-47 at 13:57-15:25. The claims do not preempt every application of conducting clinical trials, but instead address specific problems with research protocols. *See, e.g.*, *DDR Holdings*, 773 F.3d at 1257-58; *Enfish*, 822 F.3d at 1335; *Diehr*, 450 U.S. at 184, 187; *Alice*, 134 S. Ct. at 2358.

Moreover, by their very nature, the claims require transforming original compliance data into new or different data, thereby fundamentally altering the original data into other different data. For example, claims 11 and 24 require generating a "preferred compliance threshold" from analyzing particular data; generating an algorithm from particular data; and/or "translating" an algorithm into a decision rule. Appx48, Appx50. Consistent with the specification (Appx46 at 14:30-33)**,** ERT further explained that its proposed construction for decision rule as a "reformatted algorithm" fundamentally altered original data into different data. Appx619. *See, e.g., Diehr*, 450 U.S. at 192 ("On the other hand, when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect (*e.g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101."); *Bilski*, 130 S. Ct. at 3227 ("This Court's precedents establish that the machine-or-transformation test is a useful and important clue, an investigative tool for determining whether some claimed inventions are processes under § 101."); *Ultramercial*, 772 F.3d at 716 (while no longer the sole test, the machine or transformation test "can provide a 'useful clue' in the second step of the Alice framework."); *Card Verification Solutions, LLC v. Citigroup Inc*., No. 13 C 6339, 2014 U.S. Dist. LEXIS 137577, at *13 (N.D. Ill. 2014) ("But here, the claimed

invention goes beyond manipulating, reorganizing, or collecting data by actually adding a new subset of numbers or characters to the data, thereby fundamentally altering the original confidential information."); *Chamberlain Grp., Inc. v. Linear LLC*, No. 14-cv-05197, 2015 U.S. Dist. LEXIS 87876, at *30-31 (N.D. Ill. 2015) (the claims satisfy "the transformation prong of the test, as the controller responds to the status change request by moving the barrier e.g., from an open to a closed position—thereby transforming the state of the movable barrier").

The District Court's reliance on *OIP* and *Ultramercial* for its step two analysis is misplaced. This Court's discussion of these two cases in *Bascom* makes clear that *OIP* turned on confirmation in the intrinsic record "that the invention was simply the generic automation of traditional price-optimization techniques," and that in *Ultramercial* the claims "preempted all use of the claimed abstract idea on the Internet." 2016 U.S. App. LEXIS 11687 at *26. Moreover, this Court observed that in both *OIP* and *Ultramercial* an abstract idea was simply implemented on generic computer components without providing a specific technical solution beyond conventional use of generic computer concepts. *Id*.

The *DDR Holdings* case further supports patent eligibility of the '180 claims. That case indicates that claims which (1) do not merely recite a routine or conventional use in the field and (2) do not attempt to preempt every application in the field but provide a technologic solution to a unique problem in the field are

patent eligible. 773 F.3d at 1259. There, this Court determined that the claims at issue were patent eligible because (1) "the claims recite an invention that is not merely the routine or conventional use of the Internet" and (2) the claims "do not attempt to preempt every application . . ." but rather provide an "inventive concept for resolving this particular Internet-centric problem." *Id.* This underlying proposition is one not confined to the Internet field. Here, the '180 patent claims provide an inventive concept for resolving a particular problem unique to clinical drug trials and do not preempt every application of conducting clinical drug trials.

III. The '519 And '605 Patent Claims are Patent Eligible Subject Matter

A. The Claims are Directed to a Patent Eligible Concept Under Step One

For its patent eligibility assessment, the District Court identified method claim 1 of the '519 patent as representative of all '519 ***and*** '605 claims and found the '605 claims to be patent ineligible for the same reasons as the '519 claims. Appx19-21. It determined that claim 1 is directed to an abstract idea, because "classifying clinical trial results by obtaining data using a portable device and comparing the same to a norm" is a common human organizational method or longstanding business practice attributed to the claims in that district's *Erie* decision. Appx15. *See Erie*, 2015 U.S. Dist. LEXIS 129153 at *55. Specifically, the District Court characterized claim 1 as a two-step method for classifying clinical trial results in which (1) participants enter "evaluability data" on an

electronic device (2) which data is then compared to a norm to classify clinical trial results. Appx19. The Court further characterized '605 method claim 1 as merely adding a third step of "analyzing the classified clinical trial results" and the '519 and '605 independent "computer readable medium" claims as adding nothing. Appx20-21. The District Court did not adopt ERT's proposed construction for "evaluability data categories" because it believed that ERT had not explained how it would alter the Section 101 analysis. Appx9.

The District Court erred by failing to credit ERT's proposed construction for "evaluability data categories" and describing the claims at an unduly high level of abstraction which it wrongly equated with the conventional practice similar to that in *Erie*. *See, e.g., Enfish*, 822 F.3d at 1337 (too high level of abstraction); *Bancorp Serv., L.L.C. v. Sun Life Assur. Co. of Canada (U.S.)*, 687 F.3d 1266, 1273-74 (Fed. Cir. 2012) (it "will ordinarily be desirable—and often necessary—to resolve claim construction disputes prior to a §101 analysis, for the determination of patent eligibility requires a full understanding of the basic character of the claimed subject matter."). ERT explained to the District Court that its proposed construction mattered because it showed that the invention is not akin to routine patient data entry which can be done with a pen and paper, but rather is transformative. Appx542, Appx547, Appx549-550; Appx618-619. The specification supports this construction and explanation and does not contain any

suggest that this technique is routine or conventional. *See, e.g.*, Appx63, Appx68, Appx69, '519 patent at 2:7-17, 11:50-12:38, 13:34-44; Appx82, Appx87, Appx88, '605 patent at 2:10-19, 11:63-12:60, 13:38-48. Although urged to do so (Appx606), the District Court failed to accept ERT's proposed construction and the clear evidence in the specification as true under Rule 12(b)(6) standard. The claims focus on a specific way that uses evaluability data, which includes evaluability data categories, and performs a comparison of such data from the evaluability data categories to classify clinical trial results based on compliance type that in turn permits analysis of participants with a similar type of compliance. Appx70-71; Appx89-90.

Thus, the '519 and '605 claims each use a specific way to solve a technologic problem unique to clinical trials and is not directed to an abstract idea. There is not any evidence in the intrinsic record, or the *Erie* decision on which the District Court relies, that this specific way was well-known, routine, or conventional as of the time of the '519 and '605 inventions.

B. Alternatively, the Claims are Patent Eligible Under Step Two

Using claim 1 as representative, the District Court determined that the '519 and '605 claims are not patent eligible under step two because the (1) evaluability data entry step was just "routine data entry" on a generic electronic device per *Alice* and *OIP* and (2) the comparative to norm evaluability step was "the epitome

of a conventional step" per *Ultramercial*. Appx20. As such, the Court concluded that the steps lacked there is not any inventive step or transformation. *Id*. It necessarily also found that the additional analysis step in the '605 patent claims added nothing. Appx21. The District Court found that the dependent claims lacked specific transformative limitations and neither applied ERT's proposed construction nor addressed the specification. *Id.*

When properly construed and viewed in light of the specification, the claims do not merely recite a routine or conventional use in the clinical trial field and do not attempt to preempt every application in the field but provide a specific technologic solution to a unique problem in the field. Thus, the claims are patent eligible by analogy to *Diehr* and *DDR*. Further, the ordered combination of claim limitations constitutes the requisite inventive concept consistent with the specification and ERT's proposed construction, which subject matter the District Court failed to accept as true under FED. R. CIV. P. 12(b)(6). *See Bascom*, 2016 U.S. App. LEXIS 11687 at *27 (vacating and remanding Rule 12(b)(6) dismissal since nothing in the record refuted as a matter of law allegations of inventive concept residing in ordered combination).

IV. The '970 and '447 Patent Claims are Patent Eligible Subject Matter

A. The Claims are Directed to a Patent Eligible Concept Under Step One

Using each claim 1 in the '970 patent and '447 patents respectively as representative of all claims in the '970 and '447 patents, the District Court determined in a rather cursory analysis that claim 1 is directed to an abstract idea "for the same reasons as articulated above" (*i.e.*, presumably referring to the '180 patent). Appx21-23. That is, the District Court identified the abstract idea in claim 1 as the steps of obtaining data and generating and translating an algorithm into a useful rule. It then found that claim 1 was akin to the patent ineligible claims in *OIP*, *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F. 3d 1366 (Fed. Cir. 2011), and *Ultramercial*. *Id.* The District Court also found that the remaining independent claims in the '970 and '447 patents were "merely variants of claim 1" with "substantially similar steps to that articulated above." Appx22-23.

The District Court erred in classifying each claim 1 in the '970 and '447 patents as representative and describing the claims at a high level of abstraction which it wrongly equated with routine and conventional economic practice per *OIP*, *CyberSource* and *Ultramercial*. The district court also failed to credit the differing limitations in the claims, including ERT's construction of the term

"decision rule" recited in various claims.[8] When tethered to the claim language and viewed in light of the specification, the ***focus*** of the claims is a ***specific way*** to solve a ***technologic problem unique to clinical trials*** with specified algorithmic techniques that enhance individual compliance through ***predicting individual participant compliance***. The '970 and '447 specifications confirm this focus and there is not any evidence in the intrinsic record that the specific way of the claimed invention is well-known, unique or conventional. ERT urged the District Court to consider the differing claim language in light of the specification. Appx550-554. Properly applying the Rule 12(b)(6) standard, the claimed subject matter cannot be abstract since it solves problems unique to clinical trials in a specific way as to which there is not any evidence is conventional, routine or well-known. *See, e.g.*, *Bascom*, 2016 U.S. App. LEXIS 11687 at *26; *Diehr*, 450 U.S. at 184, 187; *Alice*, 134 S. Ct. at 2358; *DDR Holdings*, 773 F.3d at 1257-58; *Enfish*, 822 F.3d at 1335; *Stoneeagle,* 2015 U.S. Dist. LEXIS 85789 at *25.

Moreover, *OIP* and *Ultramercial* are inapplicable for the very reasons discussed above as to the '180 patent eligibility: the '970 and '447 patent claims are not directed to fundamental routine economic concepts and preemptive claim scope. The pre-*Alice/Mayo CyberSource* case is also inapposite as this Court

[8] The '180 and '970 patents incorporate each other's application by reference and include claims having the term "decision rule."

affirmed a § 101 summary judgment of patent ineligibility because the claims merely described a conventional approach of obtaining and using information that could be performed entirely in the human mind. *CyberSource*, 654 F.3d at 1375.

B. Alternatively, the Claims are Patent Eligible Under Step Two

Using claim 1 as representative, the District Court cursorily determined that the ’970 and ’447 claims are not patent eligible under step two because the limitations in claim 1 are not transformative of the abstract idea and do not add an inventive step. Appx22. Specifically, again relying on *OIP*, *CyberSource* and *Ultramercial*, the District Court indicated that claim 1 merely encompassed routine, conventional steps of data gathering and applying generic means to derive and convert an algorithm from such data. Appx22-23. The district court erred.

First, there is no evidence that the claimed steps, alone or in ordered combination, are well-known, routine, or conventional tasks. For example, there is no evidence that generating a “predictive algorithm” or “translating” the “predictive algorithm into at least one prediction rule” found in claim 1 of the ’970 patent are well-known or routinely performed or conventional. There is no evidence that such steps can be performed manually or merely in the human mind as it involves algorithms and translating algorithms into rules. Independent claim 1 of the ’970 patent and dependent claim 2 of the ’447 patent recite generating at

least one specified algorithm and translating that algorithm into a decision rule. Appx100; Appx114.

Second, the ordered combination of the claim limitations, particularly when viewed in light of the specification, require transforming original compliance data into new or different data, thereby fundamentally altering the original data into other different data. For example, all of the claims of the '970 patent require "generating" an algorithm or a spectrum of noncompliance representative by using particular sets of data and/or "translating" the algorithm into a rule. Appx100 at 10:42-14:37. For the '447 patent, claim 1 requires "generating at least one algorithm for determining participant noncompliance by quantitative analysis of the historical participant compliance data;" claim 16 requires "performing a statistical analysis of the historical compliance data for each clinical trial site to predict compliance in a future clinical trial;" and claim 23 requires "performing a quantitative analysis of the data to identify whether the participant is likely to produce data in compliance with research protocol in the future." Appx114. Such claims clearly meet the transformation test as the claimed inventions require transformation of particular data into other particular different data—*i.e.*, fundamentally altering the original data. *See, e.g., Diehr*, 450 U.S. at 192; *Bilski*, 130 S. Ct. at 3227; *Ultramercial*, 772 F.3d at 716; *Card Verification Solutions, LLC v. Citigroup Inc.*, No. 13 C 6339, 2014 U.S. Dist. LEXIS 137577, at *13

(N.D. Ill. 2014); *Chamberlain Grp., Inc. v. Linear LLC*, No. 14-cv-05197, 2015 U.S. Dist. LEXIS 87876, at *30-31 (N.D. Ill. 2015).

Third, the claims of the '970 and '447 patents provide inventive concepts—which are specific and concrete—for resolving a particular problem in clinical trials and thus do not preempt every application of conducting clinical trials. *See, e.g.*, *DDR Holdings*, 773 F.3d at 1257-58; *Enfish*, 822 F.3d at 1335; *Diehr*, 450 U.S. at 184, 187; *Alice*, 134 S. Ct. at 2358.

Ultimately, a fundamental error that pervades the District Court's analysis its failure to accept as true the evidence in the intrinsic record while improperly substituting extraneous general "evidence" from prior cases as to routine, conventional and well-known economic practices. *See Bascom*, 2016 U.S. App. LEXIS 11687 at *27; *TLI*, 823 F.3d at 613-14. When properly considered, the claims as a whole and the intrinsic evidence (*e.g.*, patent specifications) indicate that the subject claims are patent eligible as a matter of law or at a minimum pass muster under the Rule 12(b)(6) standard.

CONCLUSION

Based on the above, the District Court's order dismissing this action should be reversed, the claims should be concluded to be patent eligible subject matter and the action should be remanded so that it can proceed.

September 6, 2016

/s/ Edward G. Poplawski
Edward G. Poplawski

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Counsel for Appellant
eResearchTechnology, Inc.

ADDENDUM

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

ERESEARCHTECHNOLOGY, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 15-918
	)	Hon. Nora Barry Fischer
CRF, INC, d/b/a CRF HEALTH	)	
	)	
Defendant.	)	
	)	
	)	
	)	
	)	

ORDER

AND NOW, this 10th Day of May, 2016, for the reasons detailed in the accompanying Memorandum Opinion,

IT IS HEREBY ORDERED that Defendant's Motion to Dismiss, Pursuant to Rule 12(b)(6) [24] is GRANTED.

IT IS FURTHER ORDERED that this suit shall be DISMISSED for failure to state a claim upon which relief can be granted. The Clerk of Court shall mark this case CLOSED.

s/ Nora Barry Fischer
Nora Barry Fischer
United States District Judge

cc/ecf: All counsel of record.

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

ERESEARCHTECHNOLOGY, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 15-918
	)	Hon. Nora Barry Fischer
CRF, INC, d/b/a CRF HEALTH	)	
	)	
Defendant.	)	
	)	
	)	
	)	
	)	

MEMORANDUM OPINION

I. Introduction

Plaintiff eResearchTechnology, Inc. ("ERT") filed suit against Defendant CRF, Inc., d/b/a CRF Health ("CRF") on July 15, 2015, and filed an amended complaint on October 22, 2015, alleging that CRF's products infringe five of Plaintiff's patents.[1] (Docket Nos. 1, 18). Presently before the Court is Defendant's Motion to Dismiss, Pursuant to Rule 12(b)(6) and related brief, (Docket Nos. 24–25), Plaintiff's response thereto, (Docket No. 29), Defendant's Reply, (Docket No. 34), and Plaintiff's Sur-Reply, (Docket No. 35). The Court has also had the benefit of hearing and oral argument which occurred on January 29, 2016 and March 10, 2016. (Docket Nos. 36, 38). For the following reasons, Defendant's Motion to Dismiss, Pursuant to Rule 12(b)(6) [24] is GRANTED.

[1] Plaintiff asserts Patent Nos. 8,065,180 (the '180 Patent); 8,145,519 (the '519 Patent); 8,433,605 (the '605 Patent); 6,879,970 (the '970 Patent); and 7,415,447 (the '447 Patent) against the Defendant. (Docket No. 18-1 to 18-5).

II. Background

Plaintiff ERT is a Delaware corporation with its principal place of business in Pittsburgh, and is a leading cloud platform solutions provider for clinical trials. (Docket No. 18 at 2). ERT advertises that its services and products improve the accuracy and reliability of patient data within the clinical drug trial process. (Docket No. 29 at 1). Defendant CRF is likewise a Delaware corporation, but with a principal place of business in Plymouth Meeting, Pennsylvania. (Docket No. 18 at 2). CRF competes with ERT, and similarly provides mobile technology and services in the clinical trial space. (Docket No. 29 at 1–2).

Participant noncompliance with clinical drug trials is expensive and problematic for pharmaceutical companies trying to navigate the drug approval process. (*See* Docket No. 18-1 at 1:23–48). In the past, trial participants were given paper-based diaries to record their medical information during the course of a clinical trial, but that method of collecting data proved error prone. (*Id.*). Additionally, evaluating participant compliance using the paper-based diaries itself was complicated. (*Id.*). In response, clinical drug trial companies like ERT and CRF started offering electronic solutions to help pharmaceutical companies better record and analyze trial participant data. (*See* Docket No. 29-2; *also* CRF Health (last visited May 6, 2016) http://www.crfhealth.com/platform/; *PRO eCOA Scientific Services*, ERT (last visited May 6, 2016) https://www.ert.com/ecoa/pro-ecoa-scientific-services/). The benefits of using an electronic system appear to be substantial both in terms of cost-savings and increasing the quality of the clinical drug trial process. (*See* Docket No. 29-2). Accordingly, both parties have a strong incentive to police their intellectual property assets; hence, Plaintiff filed the instant lawsuit.

Plaintiff is the owner of the five patents-in-suit, *i.e.*, the ’180, ’519, ’605, ’970, and the ’447 Patents, which are collectively directed to improving clinical trials. (Docket No. 18 at ¶ 2).

Plaintiff asserts that Defendant infringes its patents, and particularly accuses Defendant of infringing them, both directly and indirectly, by way of providing and inducing others to use Defendant's "'eCOA' solution."[2] (Docket No. 18 at ¶ 20).

In the instant motion to dismiss, Defendant contends that Plaintiff's patents are not patent-eligible, and thus, Defendant cannot be found liable for infringement. (Docket No. 24). Plaintiff counters by arguing that its patents are patent-eligible and that Defendant has infringed same. (Docket No. 29).

III. Procedural Posture

Plaintiff initiated this lawsuit against Defendant on July 15, 2015, alleging that the Defendant infringed the '180, '519, and '605 Patents. (Docket No. 1). Shortly thereafter, Plaintiff filed an amended complaint, asserting the '970 and '447 Patents as well. (Docket No. 18). Defendant filed the instant Motion to Dismiss on November 5, 2015, (Docket No. 24), and the parties briefed same. (Docket Nos. 25, 29, 34, 35). As noted, the Court conducted Motion Hearings. (Docket Nos. 36, 38). Hence, the matter is now ripe for disposition.

IV. Legal Standard[3]

When reviewing a motion to dismiss pursuant to Federal Rule of Civil Procedure 12(b)(6), the court must "accept all factual allegations as true, construe the complaint in the light most favorable to the plaintiff, and determine whether, under any reasonable reading of the

[2] Plaintiff defines Defendant's allegedly infringing product as "at least the eCOA solution, alone, in combination, or parts thereof; the parts of the eCOA solution including, but not limited to, the TrialMax Touch, TrialMax Slate, TrialMax Web, TrialMax App, TrialStudio, asma-1 PEF meter, MyGlucoHealth wirelessmeter, TrialManager, TrialMax Synapse, Project Management, Collaborative Design, Data Management, and Data Collection Networks." (Docket No. 18 at ¶20).

[3] The Court applies the legal standard articulated by the Court of Appeals for the Third Circuit when deciding this motion. *Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 713 (Fed. Cir. 2014) ("We review a district court's dismissal for failure to state a claim under the law of the regional circuit in which the district court sits.").

complaint, the plaintiff may be entitled to relief." *Eid v. Thompson,* 740 F.3d 118, 122 (3d Cir. 2014) (quoting *Phillips v. Cnty of Allegheny,* 515 F.3d 224, 233 (3d Cir. 2008)). A pleading party need not establish the elements of a *prima facie* case at this stage; the party must only "put forth allegations that 'raise a reasonable expectation that discovery will reveal evidence of the necessary element[s].'" *Fowler v. UPMC Shadyside,* 578 F.3d 203, 213 (3d Cir. 2009) (quoting *Graff v. Subbiah Cardiology Associates, Ltd.,* 2008 WL 2312671 (W.D. Pa. June 4, 2008)); *see also Connelly v. Lane Const. Corp.*, 809 F.3d 780, 790 (3d Cir. 2016) ("Although a reviewing court now affirmatively disregards a pleading's legal conclusions, it must still . . . assume all remaining factual allegations to be true, construe those truths in the light most favorable to the plaintiff, and then draw all reasonable inferences from them.") (citing *Foglia v. Renal Ventures Mgmt., LLC*, 754 F.3d 153, 154 n.1 (3d Cir. 2014)).

Nonetheless, a court need not credit bald assertions, unwarranted inferences, or legal conclusions cast in the form of factual averments. *Morse v. Lower Merion School District,* 132 F.3d 902, 906, n.8 (3d Cir. 1997). The primary question in deciding a motion to dismiss is not whether the Plaintiff will ultimately prevail, but rather whether he or she is entitled to offer evidence to establish the facts alleged in the complaint. *Maio v. Aetna,* 221 F.3d 472, 482 (3d Cir. 2000). The purpose of a motion to dismiss is to "streamline [ ] litigation by dispensing with needless discovery and factfinding." *Neitzke v. Williams,* 490 U.S. 319, 326–327 (1989).

A patent case may be dismissed based on a lack of patent-eligibility,[4] under 35 U.S.C. § 101. *See e.g., Genetic Techs. Ltd. v. Merial L.L.C.*, 2016 U.S. App. LEXIS 6407 (Fed. Cir. Apr. 8, 2016) (affirming motion to dismiss based on 35 U.S.C. § 101).

[4] There is some dispute regarding what standard of review should be applied to motions to dismiss for lack of patent-eligibility. *Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *51-53, n.37 (W.D. Pa. Sept. 25, 2015) (noting differing views regarding standard of review). This Court will accept all well-

Title 35, United States Code Section 101, recites:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101. Despite the broad statutory language, "[l]aws of nature, natural phenomena, and abstract ideas are not patent-eligible." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014) (quoting *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. ___, ___, 133 S. Ct. 2107, 2116 (2013)). The aforementioned exceptions are deemed unpatentable because otherwise one could "pre-empt" an entire field by monopolizing fundamental building blocks related thereto. *See Alice*, 134 S. Ct. at 2347; *Bilski v. Kappos*, 561 U.S. 593, 610 (2010) ("A contrary holding 'would wholly preempt the mathematical formula and in practical effect would be a patent on the algorithm itself.'") (quoting *Gottschalk v. Benson*, 409 U.S. 63, 72 (1972)). Further, such pre-emption "might tend to impede innovation more than it would tend to promote it, thereby thwarting the primary object of the patent laws." *Alice*, 134 S. Ct. at 2354 (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012)); *see* U.S. CONST., Art. I, § 8, cl. 8 (Congress "shall have Power . . . To promote the Progress of Science and useful Arts") (internal quotations omitted). Courts, however, must distinguish between patents that attempt to claim the "building blocks of human ingenuity," and those that use said building blocks to create something more, thereby transforming them into patent eligible inventions. *Alice*, 134 S. Ct. at 2354 (citing *Mayo*, 132 S. Ct. at 1303).

With the forgoing in mind, the Supreme Court has set out a two-part test for distinguishing whether a patent claims patent-ineligible subject matter. First, a court must

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pleaded facts as true, but give no deference to legal conclusions. *Id.* ("Assessing a complaint at the Motion to Dismiss stage requires courts to accept all 'well-pleaded facts as true,' but legal conclusions warrant no deference.") (quoting *Fowler v. UPMC Shadyside*, 578 F.3d 203, 210-211 (3d Cir. Pa. 2009)).

determine "whether the claims at issue are directed to one of those patent-ineligible concepts." *Id.* If the court determines that a patent is so directed, then as a second step it must ask "what else is there in the claims before [the court]." *Id.* To answer the question in the second step, the court must consider "the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent eligible application." *Id.* The second step of the analysis is "a search for an inventive concept—*i.e.*, an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the ineligible concept itself." *Id.* at 2355.

V. Discussion

A. Procedural Considerations

Plaintiff initially objects to the Court evaluating Defendant's motion to dismiss, asserting that the Court cannot rule on the motion without engaging in claim construction, and that the Court cannot use representative claims to consider the patent-eligibility of the patents-in-suit. (Docket No. 29 at 1).

1) Claim Construction

Plaintiff's argument that claim construction is necessary prior to resolving Defendant's motion is unpersuasive. Although claim construction is sometimes desirable, it is not necessary. *See Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *86 ("[T]he Federal Circuit seems to have concluded that claim construction is desirable, unless in reviewing the patents at issue, a district court concludes that it isn't."); *Bancorp Servs., L.L.C. v. Sun Life Assur. Co. of Canada (U.S.)*, 687 F.3d 1266, 1273–74 (Fed. Cir. 2012); *Content Extraction & Transmission LLC v. Wells Fargo Bank, N.A.*, 776 F.3d 1343, 1349 (Fed. Cir. 2014) ("[C]laim construction is not an inviolable prerequisite to a validity determination under §

101."). If the basic character of the subject matter is readily ascertainable, the terms are defined within the patent itself, or they are synonyms to well-known concepts, the Court does not need to engage in claim construction prior to deciding the issue of patentability. *Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *86 (citing *MicroStrategy Inc. v. Apttus Corp.*, 118 F. Supp. 3d 888, 891 n.4 (E.D. Va. 2015) ("Claim construction is not necessary to dismiss patent claims at the 12(b)(6) stage or on a 12(c) motion.")). If there are any "factual disputes" during the course of the Court's analysis at the motion to dismiss stage, the Court can remedy same by resolving any such disputes in Plaintiff's favor. *Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *85 (citing *Content Extraction*, 776 F.3d at 1349).

If a party asserts that claim construction is needed, it should (1) identify for the Court claims that need to be construed, and (2) explain how construction of such terms could affect the Court's analysis. *CyberFone Sys., LLC v. CNN Interactive Group, Inc.*, 558 Fed. App'x 988, 991 n.1 (Fed. Cir. 2014) ("*CyberFone* argues that claim construction must precede the § 101 analysis, but does not explain which terms require construction or how the analysis would change. It merely points to claim language that we consider here. There is no requirement that the district court engage in claim construction before deciding § 101 eligibility."); *Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *88 ("Plaintiffs had ample time in their extensive briefing and during the marathon oral argument to the Court to identify any claim terms they believed required construction *and* to then proffer preferred constructions to the Court. They did not do that. While Plaintiffs have generally referenced terms that they thought may require construction, they have not proffered any proposed constructions or explained how

any proposed construction would affect the analysis.") (citing *CyberFone*, 558 Fed. App'x at 991 n.1) (emphasis in original).

Plaintiff argues that claim construction is necessary in this case, "to obtain a full understanding of the basic character of the claimed subject matter." (Docket No. 29 at 5). Plaintiff has identified two terms, "decision rule" from the '180 Patent, and "Evaluability data categories," from the '519 and '605 Patents, to prove that claim construction must occur prior to the Court's § 101 analysis. (*Id.* at 5). Yet, Plaintiff has not explained to the Court how construction of those terms would alter the Court's § 101 analysis. A conclusory recitation that claim construction is necessary for the Court to fully apprehend the nature of the claims cannot, without some factual basis, prevent the Court from engaging in a pre-claim construction § 101 analysis. *See Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *88. Moreover, Plaintiff's proposed constructions are uncontested. (Docket No. 34 at 2 n.2). Having reviewed the claims, the proposed constructions, and considered both parties' arguments, the Court finds that further claim construction is not needed prior to resolving the instant motion to dismiss.

2) Representative Claims

Plaintiff next contends that the Court cannot consider representative claims to evaluate the instant Motion to Dismiss. (Docket No. 29 at 1). To the contrary, a Court may evaluate representative claims when ruling on a motion to dismiss premised on § 101. *See e.g.*, *Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *84 (citing *Content Extraction*, 776 F.3d at 1348). If a patent holder objects to such treatment, it bears the burden of persuading the Court that its claims warrant independent review. *Id.* In such an instance, the Court should then review the claims to determine their similarity. *Id.* Given that

there are five patents-in-suit, the Court will consider whether to utilize representative claims relative to each patent individually.

B. Patent-eligibility

1) The '180 Patent

The '180 Patent contains thirty-four claims, eight of which are independent. (Docket No. 18-1). Claim 1 of the '180 Patent generally describes a method of determining whether action is needed in a clinical trial and comprises the following steps:

1. Obtain past data;
2. Apply quantitative analysis to past data to derive a "compliance threshold";
3. Obtain new subject data; and
4. Compare the new subject data to the "compliance threshold" to determine whether some action should be taken.

(Docket No. 18-1 at 15:40–16:36).[5] Independent claim 4 is similar to Claim 1, but substitutes the "compliance threshold" with a "predictive algorithm" and adds a step of converting the new

[5] Claim 1 recites:

> **A method of determining if action is needed regarding subject compliance** during a current clinical trial, wherein said current clinical trial comprises a group of subjects participating in said current clinical trial, comprising the steps of:
>
> **providing data on timeliness of a data entry from a previous clinical trial** and either a) historical subject compliance data from said previous clinical trial or b) historical protocol data from said previous clinical trial, wherein said historical subject compliance data comprise data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state, and wherein said historical protocol data comprise a question posed to a subject, a frequency of prompting of a subject during a day or week, an amount of time allotted for a subject to respond to a question, or a condition mandating removal of a subject from data analysis or from participation in a clinical trial;
>
> **generating a preferred compliance threshold** for use during said current clinical trial by quantitative analysis of said data on timeliness of a data entry from said previous clinical trial and either a) said historical subject compliance data from said previous clinical trial or b) said historical protocol data from said previous clinical trial; and
>
> **obtaining subject compliance information** from a subject in said group of subjects participating in said current clinical trial comprising using a portable electronic device capable of displaying information and receiving and storing input from a user to obtain

"predictive algorithm" into a "decision rule."[6] (Docket No. 18-1 at 16:42–17:5). Claim 11, is essentially identical to Claim 4 with the addition that it performs the functions specified in Claim 4 on a "portable electronic device," and that it defines some of the actions to be taken in the final step. (*Id.* 18-1 at 17:33–18:14). Independent claims 19 and 21 mirror the steps set forth in claims 1 and 11, but do so as a "computer readable medium," and add a step "prompting said action," referenced in the prior claims. (*Id.* 18-1 at 18:44–19:39, 19:43–20:29). Independent claims 22 and 23 incorporate substantially the same steps as claims 19 and 21, but generate "a spectrum of compliance," a "predictive algorithm," instead of a "compliance threshold" or "algorithm." (*Id.* at 20:30–21:24, 21:25–22:12). Independent claim 24 is virtually identical to claim 21, but without the prompting step. (*Id.* at 22:12–65). The dependent claims merely include specific applications of the terms included in the independent claims. (*See* Docket No. 18-1). Accordingly, claim 1 of the '180 Patent is representative.

> said subject compliance information from said subject in said group of subjects participating in said current clinical trial; and
>
> **comparing said subject compliance information from said subject** in said group of subjects participating in said current clinical trial **to said preferred compliance threshold to determine if said action is needed** for said subject in said group of subjects participating in said current clinical trial, wherein said action comprises removing all or part of data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of the data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on the compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in the monitoring and correcting of subject compliance.

(Docket No. 18-1 at 15:40–16:36) (emphasis added).

[6] As there is no contest, the Court adopts Plaintiff's proposed claim construction for "decision rule" to mean "reformatted algorithm." (Docket No. 29 at 5).

a) Alice Step 1

The parties have presented competing views as to on how the Court should decide whether claim 1 is directed to an abstract idea. Plaintiff contends that the Court should look to the purpose of the invention, and suggests the purpose is "to determine if action is needed to increase subject compliance during a clinical trial, in order to increase the reliability and usability of clinical trial results, which would ultimately reduce clinical trial costs, time to complete the clinical trial, and time to get a drug or medical device to market." (Docket No. 29 at 9) (citing Docket No. 18-1 at 1:61–2:3). Defendant argues that distilling the purpose of the invention is not the test for whether a patent is directed to an abstract idea, and instead articulates its version of the nature of the claim as "directed to the simple abstract idea of determining whether a clinical trial participant is entering his data on time consistent with past experience, *i.e.*, 'historical data' and, if not, calling to remind him." (Docket No. 25 at 10).

Whether a claim is directed to an abstract idea is an inquiry that can be considered as one of identifying the "heart of the patented invention/true nature of the claim." *Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *55. As noted above, "'preexisting, fundamental truth[s]' such as mathematical equations, and [] 'method[s] of organizing human activity' or 'longstanding commercial practice[s]' like intermediated settlement or risk hedging" are some examples of abstract ideas. *Id.* (quoting *Alice*, 134 S. Ct. at 2356). Understanding the purpose of an invention may aid in identifying the underlying nature of the claim. *See e.g.*, *Cal. Inst. of Tech. v. Hughes Communs., Inc.*, 59 F. Supp. 3d 974, 991 (C.D. Cal. 2014); *Stoneeagle Servs. v. Pay-Plus Solutions, Inc.*, 113 F. Supp. 3d 1241, 1250 (M.D. Fla. 2015); *DataTern, Inc. v. MicroStrategy, Inc.*, 2015 U.S. Dist. LEXIS 118530, at *26 (D. Mass. Sept. 4, 2015); *TimePlay, Inc. v. Audience Entm't LLC*, 2015 U.S. Dist. LEXIS 174781, at *18 (C.D. Cal. Nov. 10, 2015). But, the purpose of the invention is not dispositive on the issue of what defines the

"heart" of the patent and cannot render an otherwise abstract idea patent-eligible. *Parker v. Flook*, 437 U.S. 584, 595 n.18 (1978) ("Very simply, our holding today is that a claim for an improved method of calculation, even when tied to a specific end use, is unpatentable subject matter under § 101."); *Bilski*, 561 U.S. at 610–11 ("*Flook* stands for the proposition that the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment' or adding 'insignificant postsolution activity.'") (citing *Diamond v. Diehr*, 450 U.S. 175, 191–92 (1981)).

Moreover, some Courts have found that since computer programs generally comprise sets of instructions or algorithms, they are generally directed to an abstract idea. *See e.g.*, *SRI Int'l, Inc. v. Cisco Sys.*, 2016 U.S. Dist. LEXIS 48092, at *11–12 (D. Del. Apr. 11, 2016) ("Because computer software comprises a set of instructions, the first step of *Alice* is, for the most part, a given; *i.e.*, computer-implemented patents generally involve abstract ideas."); *Intellectual Ventures I, LLC v. Canon Inc.*, 2015 U.S. Dist. LEXIS 151485, at *64 (D. Del. Nov. 9, 2015).

Here, the "heart" of the invention relates to using an electronic device to obtain clinical trial data that would otherwise be collected by pen-and-paper diary, and analyzing the data to decide whether to prompt action. The individual steps comprising the method, *i.e.*, gathering data, analyzing same, and acting pursuant to that data, are similar to others that have been found to be abstract. *See e.g.*, *OIP Techs., Inc. v. Amazon.com, Inc.*, 788 F.3d 1359, 1361–62 (Fed. Cir. 2015) (finding a method comprising (1) testing prices, (2) gathering statistics about how customers reacted to the prices, (3) using that data to estimate outcomes, and (4) acting on estimated outcomes (*i.e.*, automatically selecting and offering new prices based on estimated outcome) to be directed to the abstract idea of price optimization.); *see also Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *94 (finding a method of

"gathering, storing, and acting on data based on predetermined rules" to be directed to an abstract idea).

Plaintiff nevertheless asserts that the fact that its invention is limited to clinical trials prevents it from being considered abstract. (Docket No. 29 at 9) ("Such purpose cannot be abstract, as it is seeking to solve problems uniquely within the context of conducting clinical trials"). Yet, Federal Circuit and Supreme Court precedents clearly hold that the one cannot circumvent the ban on patenting abstract ideas by attempting to limit them to a particular technological environment. *Bilski*, 561 U.S. at 610–11; *see also OIP*, 788 F.3d at 1362–63 ("And that the claims do not preempt all price optimization or may be limited to price optimization in the e-commerce setting do not make them any less abstract.") (citing *buySAFE, Inc. v. Google, Inc.*, 765 F.3d 1350, 1355 (Fed. Cir. 2014)).

Plaintiff next contends that the "specific and concrete" claim limitations save the invention from being considered abstract. (Docket No. 29 at 10) (citing *Intellectual Ventures I, LLC v. Canon Inc.* 2015 U.S. Dist. LEXIS 151485). "Specific and concrete" is not the legal standard, however, and Plaintiff implicitly concedes as much. (Docket No. 35 at 3) ("ERT never argued that "specific and concrete" is a legal standard. The adjectives describe limitations found in the claims."). Moreover, patent claims with even more specific steps have been held to be directed to abstract ideas and ultimately found patent-ineligible. *See NexusCard, Inc. v. Kroger Co.*, 2016 U.S. Dist. LEXIS 38857, at *10–12 (E.D. Tex. Mar. 24, 2016) (finding an eighteen-step claim articulating a "membership discount program" nevertheless was directed to an abstract idea). Finally, Plaintiff's reliance on *Intellectual Ventures I, LLC v. Canon Inc.*, is misplaced because the claims at issue there did not recite mathematical formula or attempt to implement any such formula, as opposed to relying on the particularity of the claims themselves. *Intellectual*

Ventures I, LLC v. Canon Inc. 2015 U.S. Dist. LEXIS 151485, at *69–70. Accordingly, the Court finds claim 1 of the '180 Patent to be directed to an abstract idea.

B) Alice Step 2

Given that claim 1 of the '180 Patent is directed to an abstract idea, the Court next considers whether the claim limitations, both individually and in combination, "transform the nature of the claim into a patent eligible application." *Alice*, 134 S. Ct. at 2355 (citing *Mayo*, 132 S. Ct. 1289). "A claim that recites an abstract idea must include "additional features" to ensure "that the [claim] is more than a drafting effort designed to monopolize the [abstract idea]." *Id.* at 2357. "[T]ransformation into a patent-eligible application requires "more than simply stat[ing] the [abstract idea] while adding the words 'apply it.'" *Id.* Further, "appending conventional steps, specified at a high level of generality," was not "enough" to supply an "'inventive concept.'" *Id.* Similarly, "the mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into a patent-eligible invention." *Id.* at 2358.

Plaintiff offers many arguments for why its claims are patent-eligible despite being directed to an abstract idea. Specifically, Plaintiff contends that: (1) the claim limitations add additional inventive features sufficient to render the claims patent-eligible because they improve a technology (clinical trials) and provide enough specificity to meaningfully bind the claims; (2) the claims create a transformation sufficient to save the claims; and (3) that the claims in suit are akin to those in *DDR Holdings*. (Docket No. 29 at 10–14). Defendant disagrees with Plaintiff's contentions, and instead argues that the claim limitations merely incorporate conventional, generic steps that are insufficient to render them patent-eligible. (Docket Nos. 25, 34).

In this Court's estimation, the claim limitations, considered individually and in combination, fail to transform the otherwise abstract ideas into patent eligible applications because they merely recite common, well-known steps. The first and third limitations call for

"providing" or "obtaining" data. (Docket No. 18-1 at 15:44–16:5). Those limitations do not contain any additional inventive steps because they describe "routine data gathering techniques." *OIP*, 788 F.3d at 1363 (finding claim limitations reciting "routine data-gathering steps" did not transform an abstract idea into a patent-eligible application of same.) "[G]enerating a preferred compliance threshold" by quantitative analysis, and comparing the collected data to the threshold as required by the second step similarly does not add inventiveness because it too requires the application of conventional, well-known analytical steps. *Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 716 (Fed. Cir. 2014) ("[T]he claimed sequence of steps comprises only 'conventional steps, specified at a high level of generality,' which is insufficient to supply an 'inventive concept.'") (quoting *Alice*, 134 S. Ct. at 2357) (internal citations omitted).

The dependent claims likewise fail to transform the abstract idea into a patent-eligible application. Plaintiff contends that three dependent claims in particular, claims 6, 26, and 28, add a transformative inventive step to the patent. (Docket No. 29 at 11). Claim 6 adds the concept of "creating an evaluability database adapted to store data related to subject compliance." (Docket No. 18-1 at 17:16–18). Claim 26 employs statistical tools to generate algorithms and thresholds. (Docket No. 18-1 at 23:3–6) ("[W]herein said step of generating employs multiple linear regression, discriminant function analysis, logistic regression, neural networks, classification trees or regression trees."). And, claim 28 defines specific data to be used for purposes of data analysis. (Docket No. 18-1 at 23:10–18) ("[W]herein said historical subject compliance data further comprise data on whether a subject had a relationship with a doctor or other medical professional, data on a number or percent of prompts not replied to by a subject, data on a subject's sleep/wake cycle, data on whether a subject had a bowel movement, data on an amount

of time a portable electronic device is in suspend mode, data on a subject's gender, or data on a subject's location.").

Employing a database to store data does not add inventiveness. *See e.g.*, *Intellectual Ventures I LLC v. Capital One Bank (USA)*, 792 F.3d 1363, 1368 (Fed. Cir. 2015) ("[I]t is clear that the claims contain no inventive concept. The recited elements, *e.g.*, a database, . . . are all generic computer elements."). Moreover, applying traditional statistical tools to data cannot possibly provide the inventive step necessary to become patent-eligible. *OIP*, 788 F.3d at 1363 (holding that "well-understood, routine conventional activit[ies]," are insufficient to transform an abstract idea into a patent-eligible application). Finally, the specific data types referenced in claim 28 do not transform the abstract idea claimed in the patent because simply defining the data to be used therein does not supply an inventive concept. *Alice*, 134 S. Ct. at 2357. Thus, the dependent claims do not add any inventive concept that can transform the patent into patent-eligible subject matter.

In a similar vein, to the extent Plaintiff argues that the "computer readable medium" claims or the "system comprising an electronic device" claims add an inventive step, those arguments fail because applying otherwise abstract claims to a computer or translating same into a medium for use in a computer is not inventive. *See Alice*, 134 S. Ct. at 2360 ("Petitioner's claims to a computer system and a computer-readable medium fail for substantially the same reasons.").

Plaintiff next argues that the machine-or-transformation test renders the claims patent-eligible. (Docket No. 29 at 12). As an initial point, the machine-or-transformation test is not dispositive on the issue of patent-eligibility, and is instead just one factor to consider. *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1256 (Fed. Cir. 2014) ("For example, in

Mayo, the Supreme Court emphasized that satisfying the machine-or-transformation test, by itself, is not sufficient to render a claim patent-eligible, as not all transformations or machine implementations infuse an otherwise ineligible claim with an 'inventive concept.'"). In any event, the transformation upon which Plaintiff relies is insufficient to convert the abstract idea into a patent-eligible application of same. *See CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366, 1375 (Fed. Cir. 2011) ("The mere manipulation or reorganization of data, however, does not satisfy the transformation prong.").

Plaintiff's reliance on *Chamberlain* is inapposite because the transformation that occurred there had nothing to do with data. *Chamberlain Grp., Inc. v. Linear LLC*, 114 F. Supp. 3d 614, 628–29 (N.D. Ill. 2015) (finding a transformation occurred because a garage door changed from an open to a closed position). Similarly, *Card Verification Solutions, LLC v. Citigroup Inc.*, does not apply to the Plaintiff's patents because the patents-in-suit do not add new data. See *Card Verification Solutions, LLC v. Citigroup Inc.*, 2014 U.S. Dist. LEXIS 137577, at *13 (N.D. Ill. Sept. 29, 2014) ("'[T]he mere manipulation or reorganization of data … does not satisfy the transformation prong.' But here, the claimed invention goes beyond manipulating, reorganizing, or collecting data by actually adding a new subset of numbers or characters to the data, thereby fundamentally altering the original confidential information.") (quoting *CyberSource*, 654 F.3d at 1375).

Finally, Plaintiff's reliance on *DDR Holdings* is unavailing because the claims at issue do not address a problem unique to the internet. *See Intellectual Ventures I LLC v. Capital One Bank (USA)*, 792 F.3d at 1371 ("The patent at issue in *DDR* provided an Internet-based solution to solve a problem unique to the Internet that (1) did not foreclose other ways of solving the problem, and (2) recited a specific series of steps that resulted in a departure from the routine and

conventional sequence of events after the click of a hyperlink advertisement. The patent claims here do not address problems unique to the Internet, so *DDR* has no applicability."). Accordingly, the claims in the '180 Patent are not patent-eligible.

2) The '519 and '605 Patents

The '519 Patent is a continuation of the '180 Patent, and the '605 Patent is a continuation of the '519 Patent; therefore, they share a common specification and priority date with the '180 Patent. (Docket Nos. 18-2, 18-3). The '519 Patent contains sixty-three claims, three of which are independent. (Docket No. 18-2). Claim 1 of the '519 Patent is representative and puts forth a two-step method for "classifying clinical trial results" comprising (1) entering "evaluability" data from the participants using "an electronic device," and (2) comparing that data to a "norm" to classify the clinical trial results.[7] Independent claim 22 recites a "computer readable medium" employing the steps articulated in claim 1, and independent claim 43 provides for a "system comprising an electronic device, again comprising almost identical steps to those listed in claim 1." (Docket No. 18-2).

The '605 Patent is substantially similar to the '519 patent, and likewise contains sixty-three claims, three of which are independent. (Docket No. 18-3). Claim 1 describes a method for classifying results from a clinical trial by: (1) electronically accessing evaluability data and storing it on an "electronic device"; (2) comparing the data to a norm to classify results; and (3)

[7] Claim 1 recites: A method for classifying clinical trial results from one or more participants in a clinical trial, the method comprising:

a. Entering evaluability data from the one or more participants on an electronic device, wherein the evaluability data comprise one or more evaluability data categories; and
b. Comparing the evaluability data from the one or more evaluability data categories to a norm to classify the clinical trial results from the one or more participants in the clinical trial based on a type of compliance, wherein the classifying allows analysis of participants with a similar type of compliance.

(Docket No. 18-2 at 15:38–49).

analyzing the classified results from participants with a similar type of compliance.[8] As was the case in the '519 Patent, the two remaining independent claims are a "computer readable medium" claim and a "system" claim. (Docket No. 18-3).

Defendant contends that "it would be hard to find a clearer example of an abstract idea" than claim 1 of the '519 Patent, (Docket No. 25 at 17), and this Court agrees. Classifying clinical trial results by obtaining data using a portable electronic device and comparing same to a norm evidences a common "method of organizing human activity' or 'longstanding commercial practice[s]." *Intellectual Ventures I LLC v. Erie Indem. Co.*, 2015 U.S. Dist. LEXIS 129153, at *55 (quoting *Alice*, 134 S. Ct. at 2356). Accordingly, this Court finds that claim 1 of the '519 Patent is directed to an abstract idea.

Step two of the *Alice* inquiry fails to save these claims. As noted above, routine data gathering, even by using a "portable electronic device" does not provide the inventive step necessary to render an abstract idea patent-eligible. *Alice*, 134 S. Ct. at 2357 ("We conclude that the method claims, which merely require generic computer implementation, fail to transform that abstract idea into a patent-eligible invention."); *OIP*, 788 F.3d at 1363 ("routine data-gathering steps" did not transform an abstract idea into a patent-eligible application of same.). Additionally, comparing data to a "norm" is the epitome of a conventional step specified at a high level of generality. *See Ultramercial*, 772 F.3d at 716 (quoting *Alice*, 134 S. Ct. at 2357).

[8] Claim 1 recites: A Method for classifying results from one or more participants in a clinical trial, the method comprising:

a. electronically accessing evaluability data obtained during the clinical trial, wherein the evaluability data is from the one or more participants in the clinical trial, wherein the evaluability data is stored on an electronic device, wherein the evaluability data comprise data from one or more evaluability data categories;
b. comparing the evaluability data from the one or more evaluability data categories to a norm to classify clinical trial results from each of the one or more participants in the clinical trial based on a type of compliance; and
c. analyzing the classified clinical trial results from the one or more participants with a similar type of compliance.

(Docket No. 18-3 at 15:40–53).

Plaintiff's argument that the dependent claims provide "specific and concrete limitations," misapprehends the law, and fails to describe sufficient transformation to render the claims patent-eligible applications. *Alice*, 134 S. Ct. at 2355. The claims cited by Plaintiff incorporating quantitative analysis, (Docket No. 18-2 at 15:59–60), discussing "statistical or data mining techniques," (*Id.* at 15:61–64), defining the type of data to consider, (*Id.* at 16:1–4), or identifying the type of database to be used, (*Id.* at 16:20–21), all fail to transform the nature of the claim into a patent-eligible application. *See e.g.*, *Alice*, 134 S. Ct. at 2357; *OIP*, 788 F.3d at 1363 ("well-understood, routine conventional activit[ies]," are insufficient to transform an abstract idea into a patent-eligible application); *Intellectual Ventures I LLC v. Capital One Bank (USA)*, 792 F.3d at 1368 (holding that a database is a "generic computer element"). Accordingly, the '519 Patent is patent-ineligible.

The '605 Patent, fares no better. Given that the only substantive differences between the two patents include that the '605 patent recites "electronically accessing" the data in step one, and that it adds a third step of "analyzing the classified clinical trial results," the Court finds that for the same reasons set forth above, the '605 Patent is not patent eligible.

3) The '970 and '447 Patents

The '970 and '447 Patents are related to, but different from the '180 Patent. (Docket Nos. 18-4, 18-5). The '970 Patent describes a method of "predicting subject noncompliance" in clinical trials, and contains thirty-seven claims, ten of which are independent. (Docket No. 18-4). Claim 1 is representative and states:

> A method of predicting subject noncompliance, comprising the steps of:
>
> providing historical subject compliance data;
>
> generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance data; and

translating the at least one predictive algorithm into at least one prediction rule for use with a clinical trial.

(Docket No. 18-4 at 10:42–49). For the same reasons as articulated above, obtaining data, generating an algorithm by quantitative analysis, and translating said algorithm into a more useful rule is directed to an abstract idea. *See Alice*, 134 S. Ct. at 2354 ("[A]bstract ideas are 'the basic tools of scientific and technological work.'") (citing *Myriad*, 133 S. Ct. at 2116); *OIP*, 788 F.3d at 1361–62 (finding a method comprising (1) testing prices, (2) gathering statistics about how customers reacted to the prices, (3) using that data to estimate outcomes, and (4) acting on estimated outcomes (*i.e.*, automatically selecting and offering new prices based on estimated outcome) to be directed to the abstract idea of price optimization); *CyberSource*, 654 F.3d at 1371 (finding a patent that (1) obtained information about other credit card transactions, (2) constructed a map of numbers based on transactions, and (3) used the map to determine if the transaction was valid, "fails to recite patent-eligible subject matter because it is drawn to an unpatentable mental process—a subcategory of unpatentable abstract ideas.").

The remaining independent claims are merely variants of claim 1 directed to "determining subject noncompliance," "detecting subject fraud," or describe "a medium suitable for use in an electronic device" comprising substantially similar steps to that articulated above. (Docket No. 18-4). Accordingly, the '970 Patent is directed to an abstract idea.

Turning to step two of the *Alice* inquiry, the Court finds that the claim limitations fail to transform this otherwise abstract idea into a patent-eligible application. As was the case with the '180 Patent, merely obtaining data, applying statistical tools to said data to derive an algorithm, and converting said algorithm by generic means does not add an inventive step. *See OIP*, 788 F.3d 1363 ("routine data-gathering steps"); *Ultramercial*, 772 F.3d at 716 ("'conventional steps,

specified at a high level of generality,'") (quoting *Alice*, 134 S. Ct. at 2357). Thus, the '970 Patent is not patent-eligible.

The '447 Patent is a continuation-in-part of the '970 Patent, and shares a substantially similar specification. (Docket No. 18-5). Claim 1 of the '447 Patent is representative and recites:

> A computer implemented method of determining noncompliance of a participant in a clinical trial, comprising the steps of:
> providing historical participant compliance data;
> generating at least one predictive algorithm for determining participant noncompliance by quantitative analysis of the historical participant compliance data;
> applying the at least one algorithm to determine participant compliance; and
> outputting notice of noncompliance.

(Docket No. 18-5 at 15:4–13). Not much differentiates the '447 Patent from the '970 Patent. That the '447 patent attempts to "determine" noncompliance or "predict success," as opposed to "predict noncompliance," does not demonstrate to the Court that the patent is not directed to an abstract concept or otherwise includes sufficient inventive additions to find it to be patent-eligible. Thus, the Court finds the '447 Patent patent-ineligible for the same reasons articulated above. *See Alice*, 134 S. Ct. at 2354; *OIP*, 788 F.3d at 1361–62; *CyberSource*, 654 F.3d at 1371; *Ultramercial*, 772 F.3d at 716.

VI. Conclusion

For the forgoing reasons, Defendant's Motion to Dismiss, Pursuant to Rule 12(b)(6) [24] is GRANTED. An appropriate Order follows.

s/ Nora Barry Fischer

Nora Barry Fischer
United States District Judge

cc/ecf: All counsel of record.

US008065180B2

(12) **United States Patent**
Hufford et al.

(10) **Patent No.: US 8,065,180 B2**
(45) **Date of Patent: Nov. 22, 2011**

(54) **SYSTEM FOR CLINICAL TRIAL SUBJECT COMPLIANCE**

(75) Inventors: **Michael Hufford**, San Diego, CA (US); **David Peterson**, Scotts Valley, CA (US); **Jean A. Paty**, Pittsburgh, PA (US); **Saul Shiffman**, Pittsburgh, PA (US)

(73) Assignee: **invivodata®, Inc.**, Pittsburgh, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1347 days.

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(58) **Field of Classification Search** 705/2, 3, 705/4; 365/230.03; 600/529
See application file for complete search history.

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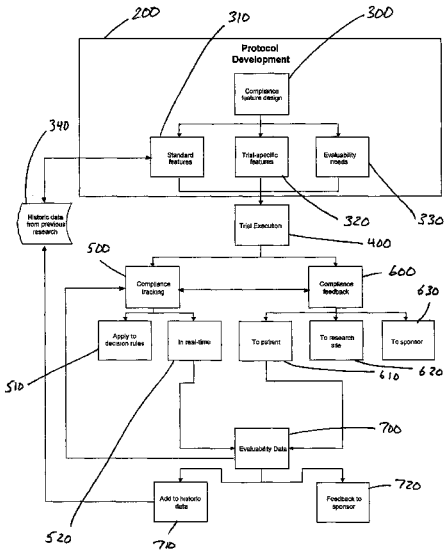
(57) **ABSTRACT**

The present invention is designed to develop research protocols for clinical trials. The invention also can track and enhance subject compliance with a research protocol. The invention further provides evaluability data related to subject performance in the clinical trial. According to an alternative embodiment of the invention, a portable electronic device is used to query and collect data from the subject.

34 Claims, 5 Drawing Sheets



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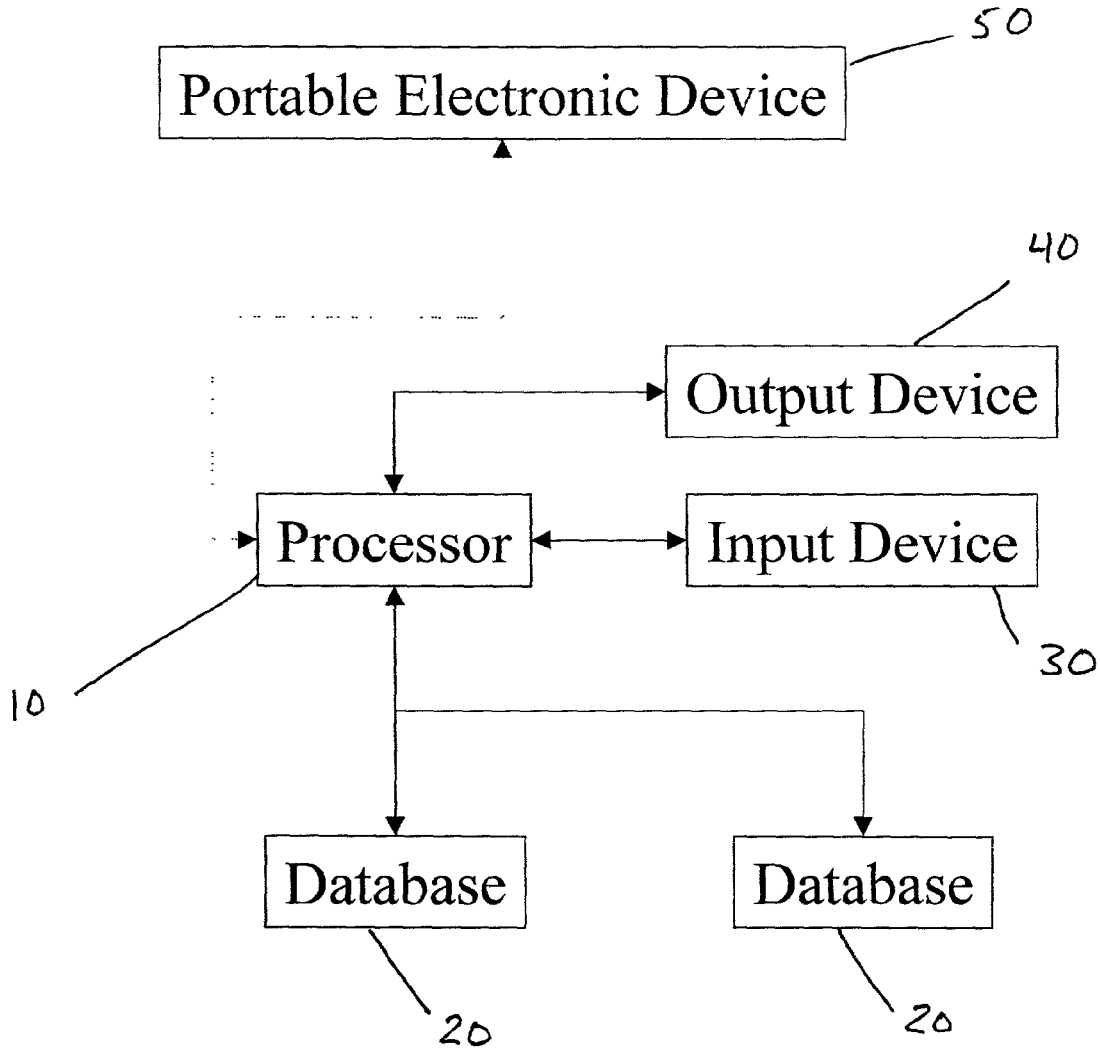
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Portable Electronic Device
40
Output Device
Processor
Input Device
30
10
Database
Database
20
20

FIGURE 1

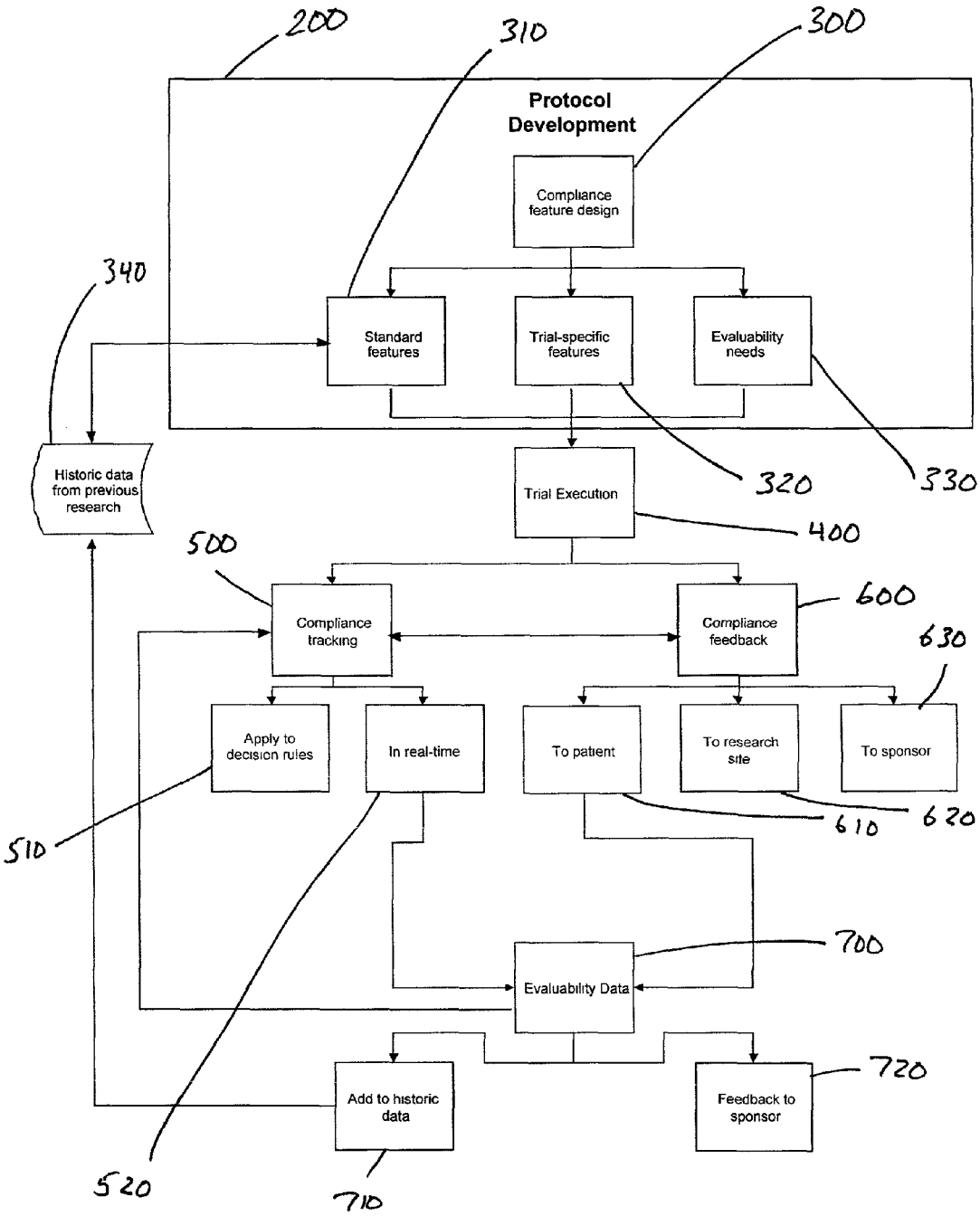

200
310
300
Protocol Development
Compliance feature design
340
Standard features
Trial-specific features
Evaluability needs
Historic data from previous research
320
330
Trial Execution
400
500
Compliance tracking
600
Compliance feedback
630
Apply to decision rules
In real-time
To patient
To research site
To sponsor
510
610
620
700
Evaluability Data
720
Add to historic data
Feedback to sponsor
520
710

FIGURE 2

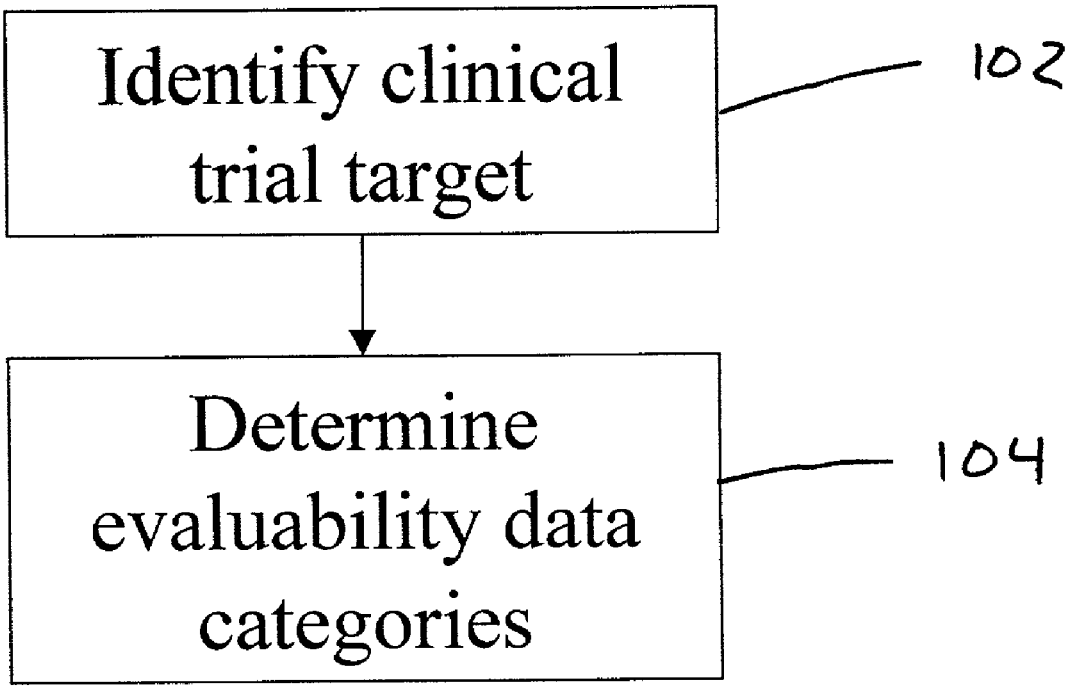

Identify clinical trial target
102
Determine evaluability data categories
104

FIGURE 3

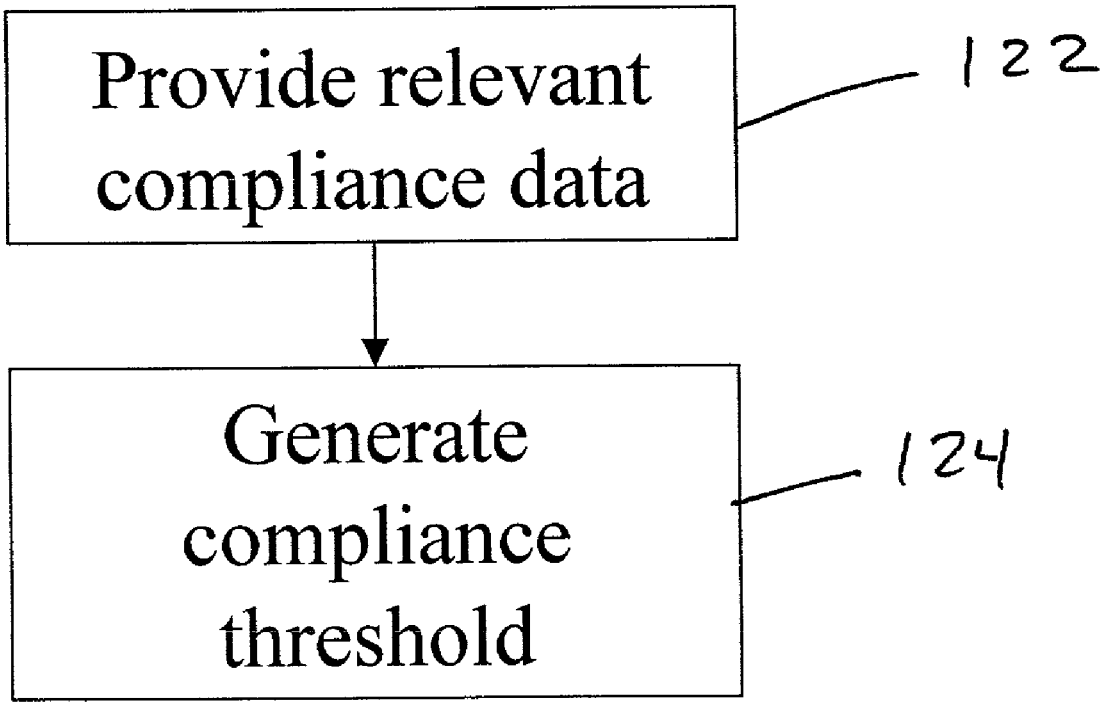

Provide relevant compliance data
122
Generate compliance threshold
124

FIGURE 4

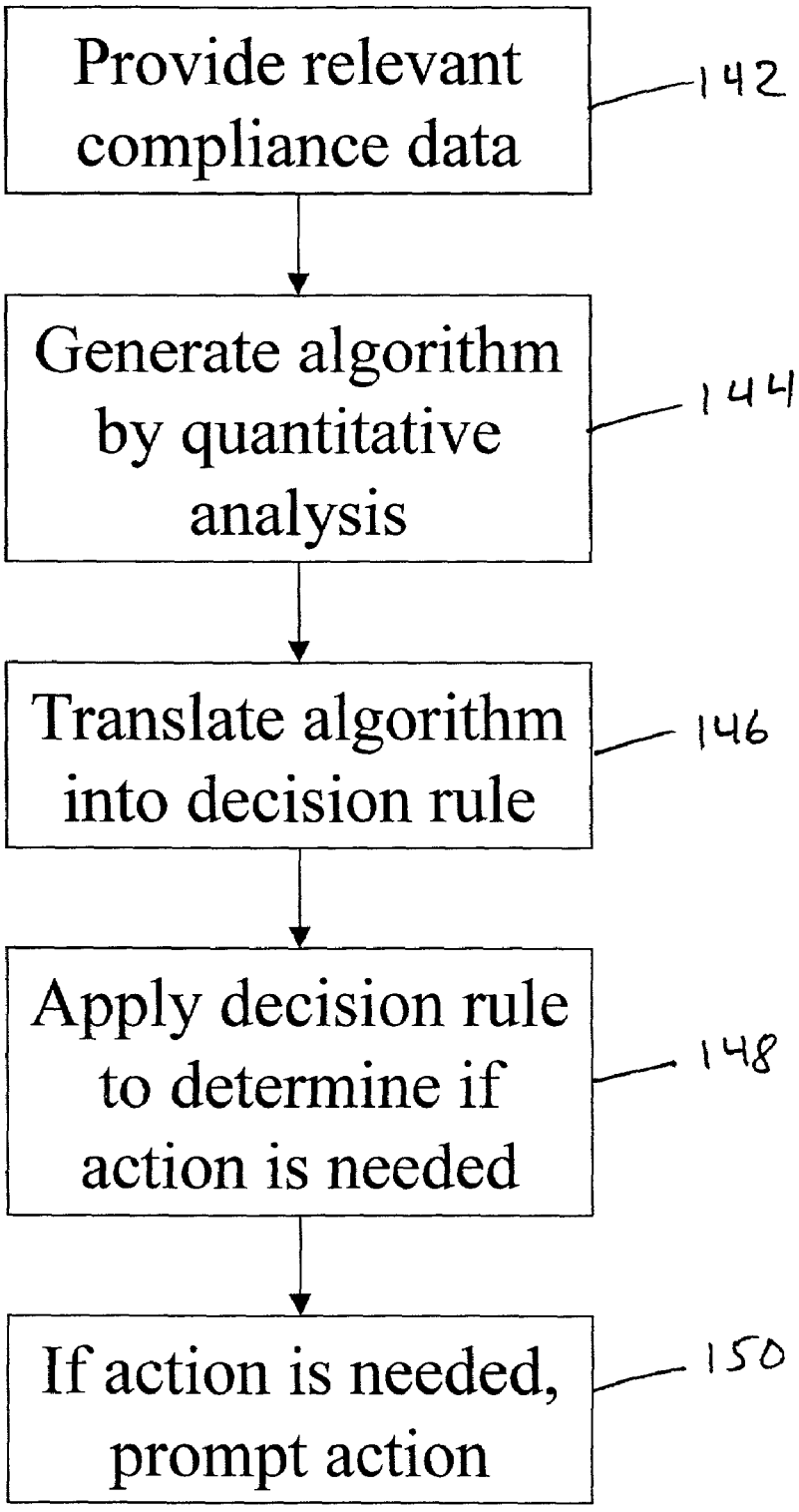

Provide relevant compliance data
142
Generate algorithm by quantitative analysis
144
Translate algorithm into decision rule
146
Apply decision rule to determine if action is needed
148
If action is needed, prompt action
150

FIGURE 5

SYSTEM FOR CLINICAL TRIAL SUBJECT COMPLIANCE

REFERENCE TO RELATED APPLICATIONS

The subject matter of this application relates to the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970, and filed on even date herewith. The aforementioned application, and the references cited therein, are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to conducting clinical trials. Specifically, the invention relates to research protocol development, management of subject behavior and distribution of evaluability data.

BACKGROUND OF THE INVENTION

Noncompliance with research protocols can be especially problematic, potentially resulting in unusable trial data. Typically, subjects are given a paper-based diary and asked to make scheduled entries regarding their illness, medication effects, as well as other data entries recording events as they happen. Subjects must keep track of the time of day, where they are in the sequence of events for any given day, and the appropriate procedures they are to follow across days. Many subjects do not complete their diaries or complete their diaries long after the events that are to be logged. Eight studies have examined compliance rates of these paper diaries by covertly collecting data about the timeliness of entries. A dramatic difference between subjects' reported versus actual compliance was observed. Whereas the paper diaries appeared to indicate high rates of compliance (88%), the actual rates of compliance were significantly lower (54%).

Evaluation of subject compliance with research protocols is often performed by examining only one variable at a time. Such evaluation is not empirically derived by quantitative analysis of existing datasets. Instead the evaluation relies on the researcher's judgment and biases to determine whether and what type of corrective action is required. Furthermore, evaluation of subject compliance with clinical trial protocols has typically not taken into account the domain of the clinical trial or the characteristics of the subjects.

SUMMARY OF THE INVENTION

The goal of clinical trials is to collect valid, reliable data on one or more conditions within a clinical trial group of subjects. Subjects in clinical trials are assigned tasks related to treatment and data collection in accordance with a research protocol. The integrity of clinical trials rests upon subjects' faithful performance of these tasks. If subjects fail to comply with the protocol, the trial will fail to yield reliable, valid trial data or results. Thus, subject noncompliance in clinical trials is a significant risk and cost to the pharmaceutical industry. Accordingly, the creation of appropriate research protocol, management and enhancement of subject behavior and effective distribution of clinical trial data is of substantial value to clinical research.

The benefits of a system that can track and enhance subject compliance in a clinical trial include: reliable, valid data; increased statistical power, reduced clinical trial costs through smaller sample sizes; reduced time to complete the clinical trial; and, ultimately, reduced time to get a drug or medical device to market.

According to one embodiment of the invention, a method of protocol development for a clinical trial is provided. The method includes the steps of identifying a clinical trial target reflecting a goal of the clinical trial, determining desired evaluability data categories to be gathered pertaining to a participant in the clinical trial, wherein an evaluability data of at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in one or more of the trial results.

According to another embodiment of the invention, a method of determining preferred targets for subject compliance is provided, having the steps of providing at least one of the group of historical subject compliance data and historical protocol data and generating at least one preferred compliance threshold by quantitative analysis of at least one of the group of the historical subject compliance data and the historical protocol data.

Another embodiment of the invention provides a method of monitoring subject compliance and having the steps of providing historical subject compliance data, generating at least one algorithm reflective of the historical subject compliance by quantitative analysis of the historical subject compliance data and the historical protocol data, translating the at least one algorithm into at least one decision rule for analyzing subject compliance information, obtaining the subject compliance information, comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a method of determining subject compliance and having the steps of providing historical subject compliance data and historical protocol data, generating a spectrum of compliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data, obtaining subject compliance information, comparing the spectrum of compliance to the subject compliance information to determine if corrective action is needed, and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a method of predicting subject noncompliance and having the steps of providing historical subject compliance data, generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance data, translating the at least one predictive algorithm into at least one prediction rule, obtaining subject compliance information, comparing the subject compliance information to the at least one prediction rule to determine if action is needed, and prompting action if the step of comparing indicates that action is needed.

A further embodiment of the invention provides a method of enhancing subject compliance and having the steps of providing historical subject compliance data, generating at least one algorithm by quantitative analysis of the historical subject compliance data, translating at least one algorithm into at least one decision rule, obtaining subject compliance information and comparing the subject compliance information to the at least one decision rule to determine if affirmative action is warranted.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a

portable electronic device capable of displaying information and receiving and storing input from a user and an alarm electrically coupled to the portable electronic device and having varying alarm tones, wherein the varying alarm tones are emitted by the alarm if the user does not comply with a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a user and an alarm electrically coupled to the portable electronic device and having a tactile alarm.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device examines the input and reviews the input for inconsistencies.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device increases an amount of prompting of the input from the participant upon an automated determination that the participant does not comply with a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device decreases an amount of prompting of the input from the participant upon an automated determination that the participant has reported a predetermined number of events other than in response to the prompting by the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a user, wherein the user is provided feedback based on the determination of whether the user has followed a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of identifying a clinical trial target reflecting a goal of the clinical trial, determining desired evaluability data categories to be gathered pertaining to a participant in the clinical trial, wherein an evaluability data of at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in at least one result of the clinical trial.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing at least one of the group of historical subject compliance data and historical protocol data and generating at least one preferred compliance threshold by quantitative analysis of at least one of the group of the historical subject compliance data and the historical protocol data.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one algorithm reflective of the historical subject compliance data by quantitative analysis of the historical subject compliance data, translating the at least one algorithm into at least one decision rule for analyzing subject compliance information and obtaining the subject compliance information. The steps further include comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data and historical protocol data, generating a spectrum of compliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data, obtaining subject compliance information, comparing the spectrum of compliance to the subject compliance information to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance data, translating the at least one predictive algorithm into at least one prediction rule, obtaining subject compliance information, comparing the subject compliance information to the at least one prediction rule to determine if action is needed and prompting action if the step of comparing indicates that action is needed.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one algorithm by quantitative analysis of the historical subject compliance data, translating the at least one algorithm into at least one decision rule and obtaining subject compliance information and comparing the subject compliance information to the at least one decision rule to determine if affirmative action is warranted.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of displaying information to the participant and prompting input from the participant, accepting the input from the participant and decreasing an amount of prompting of the input from the participant upon an upon an automated determination that the participant has reported a predetermined number of events other than in response to the prompting by the portable electronic device.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following description and apparent from the accompanying drawings.

FIG. **1** illustrates a system according to an embodiment of the present invention;

FIG. **2** provides a functional layout of one embodiment of the present invention;

FIG. **3** illustrates a method according to an embodiment of the present invention;

FIG. **4** illustrates a method according to an embodiment of the present invention; and

FIG. **5** illustrates a method according to an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The illustrative embodiment of the present invention is designed to develop research protocols for clinical trials, track and enhance subject compliance with protocol requirements and provide evaluability data related to subject performance in the clinical trial.

The illustrative embodiment involves an empirically derived set of algorithms and decision rules to predict, track and enhance subject compliance with research protocols. The illustrative embodiment uses algorithms and decision rules to provide an empirical approach for analysis of different types of subject noncompliance with research protocols. This actuarial approach to predicting and managing subject noncompliance with clinical trial protocols is consistent with empirical research demonstrating the superiority of actuarial prediction of human behavior as compared to subjective clinical judgment. According to an alternative embodiment of the invention, a portable electronic device is used to query and collect data from the subject.

As used herein "clinical trial" refers to a broad range of data collecting activities, including studies directed to monitoring of one or more conditions within a clinical trial group of subjects. One such example includes drug trials involving humans. As used herein "subject" refers to any participant in a clinical trial, whether or not the subject has any relationship to a doctor or other medical professional.

Data "evaluability" refers to the usefulness of the data for the intended clinical trial purpose. Various factors may affect data evaluability, principally the circumstances under which the data was collected and how closely the circumstances with the research protocol for the specific clinical trial.

"Trial data" or "clinical trial data" refers to data gathered for the principle purpose of the clinical trial. For example, trial data would include pain levels experienced by subjects in a pain medication clinical trial or craving levels in an anti-smoking medication clinical trial.

"Evaluability data" or "compliance data" or "compliance information" is data that relates to the circumstances under which the trial data was collected or other data pertaining to characteristics of the trial data or other evaluability data. Some examples include timeliness, consistency with other collected data, proximity of the data to an expected data range and completeness of the data.

"Historical protocol data" includes data specifying the research protocol of earlier clinical trials. Examples of historical protocol data can include questions posed to subjects, frequency of prompting of a subject during various times of the day or week, time allowed for subjects to respond to questions, requirements of subject behavior, and conditions mandating removal of a subject from specific analyses or from participation in the clinical trial.

As used herein "portable electronic device" refers to any electronic device that can be adapted for use by a subject and/or clinical staff for viewing and/or inputting information. Preferably, the portable electronic device will also have a visual, audible or tactile alarm to gain the attention of the subject. For example, a pager having a vibration alarm may be used as a portable electronic device. Further examples include, pagers with audible alarms and/or text messaging capabilities, a laptop computer or a cell phone. Preferably, according to the invention, a portable electronic device will be a handheld computer provided with a display and a data input feature, such as a touch-sensitive screen, or buttons to enable a subject to respond to questions posed on the display or to input unsolicited information. Examples of such portable electronic devices include the Palm Pilot by Palm, Inc or Windows-based devices running Pocket PC from Microsoft Corporation. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem and/or a network, such as a LAN or the Internet.

According to an embodiment of the present invention, a system is provided as shown in FIG. **1**. A processor **10** is provided and is adapted to communicate with at least one database **20**. As discussed below, the database preferably stores data related to subject compliance and associated research protocols. An input device **30** is also provided to allow the subject or another person to provide input to the processor **10**. The input device **30** may be a keyboard, a modem or other such device adapted for communication with the processor. An output device **40** is also preferably provided to receive and display information from the processor **10**. Examples of output devices **40** include a printer and a monitor.

In one embodiment of the invention, a portable electronic device **50** is provided and selectively operatively coupled to the processor **10**. The portable electronic device **50** can also include a processor and may serve as an alarm, an input device, an output device, and/or a database.

In one embodiment, the present invention includes software that resides on a portable electronic device. Preferably, the portable electronic device is a handheld portable computer.

In another embodiment, the present invention includes software that resides on a server. Optionally, the server may communicate with a computer or portable electronic device.

FIG. **2** provides a functional layout of an embodiment of the present invention. Protocol development **200** involves a review of the goals of the clinical trial to determine research protocol including subject compliance targets prior to the start of the clinical trial. Preferably, compliance targets are developed in accordance with the invention disclosed in the co-pending patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970. Optionally, protocol development **200** can involve analysis of and updates to the protocol while the clinical trial is underway. Therefore, in accordance with an optional embodiment of the present invention, protocol development **200** can occur during trial execution **400**.

The present invention preferably involves identification of compliance targets relevant to specific features of the research protocol prior to the start of the clinical trial. These compliance targets can then be used to track subject compliance. Once these compliance targets have been identified, compliance-enhancing features can optionally be developed for a specific clinical trial and can preferably be incorporated into the functionality of the portable electronic device.

It is also within the scope of the present invention to use empirically derived algorithms to determine the best compliance targets for a specific clinical trial by the use of the quantitative analysis methods of the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970.

These algorithms could identify non-intuitive, combinations of variables derived from historical data from previous clinical trials. Combinations of different compliance targets identified from other clinical trials could be used to predict a set of variables to be tracked in order to maximize an ability to detect subject noncompliance. Preferably, algorithms are translated to decision rules to ease detection of subject noncompliance.

Examples of various types of data that may be collected according to an embodiment of the invention include variables that may represent 'non-intuitive' predictors such as: gender of the subject, disease severity, the time of the year, and the day of the week.

Protocol development **200** preferably includes compliance feature design **300** to incorporate features into the research protocol to enhance subject performance in complying with the research protocol. Compliance features are preferably active during the execution of the clinical trial. Compliance features may be provided by a portable electronic device driving the protocol for subjects by guiding the subject through the protocol, not requiring the subject to remember the details of all the research protocol. For example, the portable electronic device can activate an alarm to prompt the subject to view the device. The portable electronic device can then prompt the subject to answer appropriate questions to gather information as specified by the research protocol. Optionally, the portable electronic device can modify and tailor questions based on information provided by the subject or based on input from the clinical staff. Preferably, each subject is provided with a portable electronic device and will keep the portable electronic device in their possession at all times during the clinical trial.

By the use of the portable electronic device, the present invention also allows subjects to administer self-reports of trial data including subjective reports, such as pain reduction, objective symptom reporting, such as bowel movement or asthmatic episode and cognitive measures, such as arithmetic tasks or reaction time. The electronic device may also optionally be configured to synchronize with any portable physiological measurement device to gather data from, or communicate with, the physiological device.

Moreover, portable electronic devices can optionally track all aspects of their use, resulting in a comprehensive record of subject compliance with the research protocol. A preferred embodiment of the invention allows clinical trial staff to systematically collect data regarding subject compliance by tracking a variety of different components of compliance, as well as check in compliance against empirically derived algorithms and decision rules of compliance. These empirically derived algorithms and decision rules allow the disclosed invention to examine the data for nonintuitive and complex combinations of predictors to proactively determine whether the observed pattern of interaction with the portable electronic device suggests noncompliance. The patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970, provides additional detail regarding such algorithms and decision rules.

The portable electronic device also preferably conducts ongoing compliance checks and gives the subject feedback about their performance. For example logical psychometric or other inconsistencies can be determined by the portable electronic device. Actions of the portable electronic device are preferably processed according to decision rules. The portable electronic device can also vary its behavior based on the subject's behavior. For example, prompt frequency may be delayed or increased, or louder prompts may be provided. Also, vibration or visual alerts can be generated. Evaluability data related to the activity conducted with a portable electronic device is preferably transferred from the portable electronic device to a database for collecting information from multiple portable electronic devices. Such a database is preferably, a database hosted at a central location. In one embodiment of the invention, the database is hosted on PC-based server software and is preferably adapted for communication with other computers. Additional compliance checks are preferably performed on the server and feedback is given to subjects by clinical trial staff; the feedback could be face-to-face or remote. Finally, the evaluability data is used to determine the evaluability of subject data, and screen out subjects or parts of subjects' data during the data analysis and reporting of the clinical trial data or results. Thus, the present invention is preferably utilized from beginning to end of a clinical trial.

Compliance feature design **300** includes standard features **310**, trial specific features **320**, and evaluability needs **330**. Incorporating standard features **310** within the research protocol preferably involves review of historic data from previous research **340**, including prior operations of the invention on earlier clinical trials and other sources of data involving subject compliance and, preferably, associated research protocols. Preferably, standard features **310** incorporated into the protocol will be derived in accordance with co-pending patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970, and will involve historic data from related clinical trials. For example, a clinical trial related to a cardiovascular condition will preferably develop standard compliance features **310** from historic data involving cardiovascular clinical trials.

Many types of compliance enhancing features are possible. For example, to enhance subject compliance with regular monitoring of symptom severity, varying alarm tones could be used to engender compliance. For example, if subjects are prompted using an audible 'beep' to complete a symptom report, the tone may increase in volume and/or pitch to increase the probability that subjects will complete the report. Other examples of compliance-enhancing features include allowing subjects to delay a report if they are busy. Subjects can also initiate a brief suspension of monitoring if their activity precludes completion of a report, for example, while driving. The portable electronic device could automatically re-initiate monitoring after a set amount of time has elapsed, or alternatively the subject could re-initiate monitoring. These examples do not represent an exhaustive list of compliance enhancing features of the present invention.

According to a preferred embodiment of the present invention, the following data is gathered by the use of a portable electronic device: the number of completed assessments or the ratio to expected assessments; the number or percent of prompts from the portable electronic device for data input that were not replied to by the subject; a variety of time based variables, such as for example, a sleep/wake cycle, obtained by having the portable electronic device record when subjects went to sleep and awoke each day of the clinical trial; the amount of time a subject puts the portable electronic device in a suspend mode that temporarily prevents the diary from prompting the subject for a reply; how often and for how long subjects respond to a prompt by requesting the portable electronic device delay a reply period; the frequency with which a subject abandons the portable electronic device, for example, how often does the subject's pattern of inactivity

with the portable electronic device suggest he/she has ceased complying with the research protocol.

Trial specific features **320** may also be included in compliance feature design **300** and may include specific aspects related to the current clinical trial. For example, compliance targets can also be identified based on specific characteristics of the disease state or clinical judgment of the clinical staff. For example, if subjects typically report a certain number of disease episodes per day, the present invention may target episodes per day as one variable to be tracked during the clinical trial and will automatically prompt subjects if a disease episode is not reported every 5 hours.

Evaluability needs **330** may also be incorporated in compliance feature design **300** and may involve tailoring compliance features in order to maximize evaluability data or address specific sponsor requirements. Preferably, evaluability needs **330** will be an integral part of the initial design of the research protocol. An example of an evaluability need **330** is a requirement that subject must report at least 5 disease episodes per day to be included in a particular analysis. In this example, how many disease episodes reports each day may be identified as an important variable to be tracked during trial execution.

During and/or after trial execution **400**, compliance tracking **500** is performed and involves analyzing subject behavior data and comparing it to the research protocol. Compliance tracking data, e.g. evaluability data, is gathered during the clinical trial and compared to historic norms **510** during or after the clinical by the use of decision rules. Additional detail is provided in the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970.

According to a further embodiment of the invention, algorithms can be used with decision rules to automatically generate feedback to both subjects and research staff. For example, an algorithm predicting a pattern of intermittent noncompliance with one facet of a clinical trial protocol could trigger a prompt to the subject on the portable electronic device to remain vigilant. Feedback could also be generated to the research staff to address an issue with the subject. Because the algorithms and decisions are preferably based on formal, empirical, and quantitative criteria, subjectivity can be removed from these decisions, which in turn minimizes the potential for bias.

An embodiment of the present invention preferably tracks compliance with the research protocol expected of subjects, such as timely completion of reports and compliance with the medication regimen. To successfully assess and remediate subject performance in clinical trials, the present embodiment preferably tracks compliance at several levels. If a portable electronic device is used for data entry, compliance may be tracked at the moment of data entry by determining whether or not the entry falls within acceptable parameters of the protocol. For example, is a response to a prompt required to be completed in the morning timely, or is the response delayed until the afternoon. Compliance tracking can also examine the content of the data entry itself to determine whether or not the subject is being compliant with the research protocol. For example: inconsistencies among two or more responses given; subject claiming they are in their living room and swimming. Compliance tracking can also take place over some span of time, such as for example, weekly, to examine patterns or rates of noncompliance over time. Compliance tracking can also be performed against data pertaining to the subject's behavior during the clinical trial. For example, trends in subject response times or in the responses themselves can be determined.

The present invention can optionally reduce the burden on a non-compliant subject in order to increase compliance rates by providing fewer prompts for information. Also, the present invention can reduce the number of prompts for a subject that has provided voluntary, unprompted information. In summary, the present invention can be interactive. The present invention is preferably configured to initially enhance compliance while evaluating compliance as the clinical trial progresses. Preferably, the present invention dynamically adjusts in response to the subject's behavior, in accordance with the decision rules.

Compliance feedback **600** may involve forwarding messages, activating alerts or taking some other action in order to provide information to the subject **610**, the clinical trial staff, including the research site **620**, or to the sponsor **630**. Such messages may be include, for example positive feedback, corrective feedback or a recommendation to dismiss a subject from the clinical trial.

To increase the benefit of the compliance tracking feature of the present invention, compliance feedback is preferably provided to subjects, the research site, and the clinical trial sponsor in a timely fashion. Compliance tracking and compliance feedback may be conducted in an ongoing, timely manner on the portable electronic device itself. Compliance tracking and compliance feedback can occur also occur later, after data has been transmitted to a database, such as a database on a central server. In such a case, compliance feedback instructions can be sent back to the portable electronic device to provide feedback to subjects. Feedback for subjects can optionally be directed to clinical trial staff for delivery to the subjects.

According to an embodiment of the invention, a portable electronic device or a computer, such as a workstation or a server, can automatically check incoming data against a decision rule to determine if the pattern of responses require that a compliance alarm be triggered. Optionally, other demographic variables can also be checked by a decision rule. If one or more decision rules note that a problematic pattern of noncompliance or potential noncompliance is being observed, a number of actions may be taken. Examples of such actions include: posting a message on a website to be reviewed by the sponsor or research site, sending an e-mail or other type of notification, such as an automated call, to the subjects or research site coordinator, instructing the portable electronic device to display a certain message to the subject, instructing the portable electronic device to call the site during the subject's next interaction with the device, etc. These checks can either be triggered manually or automatically upon receipt of the data from the field.

According to an embodiment of the invention, the computer can perform the compliance analyses of incoming data instead of the compliance analyses being conducted by the portable electronic device. For example, the computer can analyze incoming data and compute the ratio of missed to completed assessments. This would be appropriate if the method of collection of the data did not otherwise allow the compliance data to be generated. For example, such a method of collection may involve written forms or an instrumented device not capable of computations.

According to another embodiment of the invention, the computer can execute more extensive compliance analyses than are capable on a portable electronic device. For example, more memory or processing power may be required to use the item response theory to examine the probability that a series

of responses are likely as compared to an existing database of population norms for a given measure.

According to a further embodiment of the invention, the computer can aggregate a series of assessment data over time within or between subjects. These aggregated compliance analyses on the computer allow for greater capacity than may be capable on a portable electronic device.

According to an embodiment of the invention, the computer can provide data to be displayed. Data may be displayed at the computer itself or be transmitted to another location, such as via hardwired or wireless access to the computer, including a LAN or the Internet. The data can be processed to provide a graphical display to interested parties. Examples of those who may be interested in viewing the graphical representation of the compliance data include a site coordinator (who may be interacting with the subject), a clinical research organization (who may be responsible for study execution across a number of research locations), other agencies interested in the collection of the data, or the sponsor of the research.

According to another embodiment of the invention, the computer can provide ongoing aggregation of data across subjects to speed the time required to combine, clean, and make available final data.

The various features of the computer, such as a workstation or server, of the above embodiments of the invention may be used individually or in combination.

Subject changes in behavior in response to compliance feedback may also be assessed. That is, an embodiment of the present invention may assess subjects' behavior in response to feedback regarding their compliance with the research protocol. For example, the software can detect whether or not subjects have begun to follow the research protocol more closely as a function of having received previous feedback about their noncompliance with the protocol.

Compliance feedback can take many forms. Compliance feedback can be given to a subject at varying intervals at any location, ranging from frequent, timely feedback, to more episodic feedback based on aggregate measures of compliance. Systematic compliance feedback may be given to subjects to encourage continued compliance, remediate poor compliance, or administer rewards to subjects for their performance.

Compliance feedback may be given to the clinical trial staff. To maximize the impact of the compliance system on trial success, clinical trial staff preferably receives training in the monitoring and correcting of subject compliance according to the present invention.

In one embodiment, the present invention creates customized graphical summaries of compliance tracking data and produces standardized reports for delivery of compliance feedback to subjects, the research site and/or clinical trail staff. Research sites are instructed on how to give standardized feedback to subjects in order to remediate poor subject compliance.

The aggregation of this compliance feedback can optionally be compiled into subject and clinical trial status reports during the clinical trial. These reports are for the research site and/or sponsors, to be used in evaluating the progress of the clinical trial. These reports contain a summary of subjects' compliance with research protocol, and therefore are an indicator of data evaluability.

Compliance tracking data is timely **520** forwarded as it is collected to an evaluability database **700**. Aggregation of compliance data enhances evaluation of subjects, prompting methodologies and research sites. Aggregated compliance data also allows for subjects to be examined for evaluability analyses. Also, evaluability data may be incorporated in compliance tracking **500** decisions during the course of a clinical trial. The evaluability database **700** also can provide additional historic data **710** to be included in a historic data database **340** upon which further research protocols are developed, as appropriate. The evaluability database **700** is also preferably made available to clinical staff and research sponsors. By making the evaluability database **700** accessible to clinical trial sponsors, sponsors are able to participate in decision making regarding the management of the clinical trial as the clinical trial is conducted. Furthermore, sponsors are able to monitor the progress of a clinical trial as it proceeds.

Evaluability data can be gathered in an evaluability database: a database that contains information relevant to the evaluability or acceptability of data from each subject. Evaluability data represents data that is of significant benefit for clinical trial sponsors. The evaluability database allows clinical trial sponsors to have timely evaluability data regarding the quality and consistency of the trial data. An example of trial data is efficacy data on the impact of the drug or medical device on the subject. In other words, the evaluability data allows clinical trial sponsors to have data about the quality of the trial data.

One specific use of the evaluability database is to determine whether or not a specific subject's data would be used in an analysis. For example, an analysis may be limited to those subjects who met minimal criteria for compliance. Another specific use of the evaluability database is to determine desirable trial data for a specific subject or among multiple subjects. This use of evaluability data involves whether or not specific data points within one or more subjects' trial data would be used in an analysis. For example, among all subjects, only trial data from days when compliance met acceptance criteria may be desired. In each instance, the evaluability data becomes an important and unique source of information regarding trial data quality in a clinical trial.

Evaluability data can be aggregated to create global, as well as disease and population-specific databases. The result of this aggregation of evaluability data provides an ability to predict subject noncompliance in clinical trials. This prediction ability increases as more evaluability data is available.

Evaluability data may also be reviewed by clinical trial staff. The periodicity of the data review could range from weekly to instantaneous, optionally using wireless technology or a web site located on the Internet. During the data review, the data can be checked using algorithms or decision rules to determine whether the pattern of subject behavior up to that point in the clinical trial triggers a decision rule, which may therefore recommend a course of action. Courses of action may include, for example providing feedback to the subject, the research site, the sponsor and/or the clinical trial staff. The review may examine data over varying time intervals to determine whether some type of corrective action is necessary. By the use of the present invention, evaluability data can be reviewed for critical patterns of factors related to noncompliance or other events, such as effectiveness of compliance enhancement measures, ranging from within-day assessments to patterns extending over many months of monitoring.

The portable electronic device is also preferably adapted to communicate with another computer to allow the clinical staff to consolidate the data from all subjects in the clinical trial into one location for review or processing. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem

and/or a network, such as a LAN or the Internet. For example, by the use of the Internet or a dial-up modem connection, a subject may submit information from the portable electronic device to the clinical staff from the subject's home.

In another embodiment, a portable electronic device or a computer is adapted to communicate with clinical trial equipment used for measuring, monitoring, controlling or recording data or a process of the clinical trial. Examples of such processes include administration of medication or monitoring of heart rates. The portable electronic device or a computer preferably automatically records desired data for incorporation in the clinical trial data or compliance data. A further example of clinical trial equipment is an instrumented bottle cap, which is capable of recording and/or reporting when a bottle is opened or closed.

In another embodiment, clock synchronization can be used to synchronize data from clinical trial equipment used for measuring, monitoring, controlling or recording data or a process of the clinical trial with data collected by a computer or portable electronic device for later analysis.

In another embodiment of the invention, a paper form, such as a case report form, can be used by the subject to record data. The data can then be entered into a database by the use of a portable electronic device or other computer at an appropriate time. Examples of case report forms include hand-written forms and forms that allow for machine readable marks to be made, enabling automated scanning of the case report forms during entry of the data into a computer.

In an alternative embodiment of the present invention, the methods of the present invention may be incorporated in instructions recorded on a medium suitable for use in an electronic device, such as a computer, computer network server or a portable electronic device. The medium can include, for example, a hard disk, RAM medium, diskette, CD-ROM or other optical or magnetic storage medium. The instructions can optionally be stored on a server that can be remote from the subject and/or clinical staff member.

According to a further embodiment of the invention, a flow chart illustrating a method of protocol development of the present invention is set forth in FIG. **3**. First, a clinical trial target reflecting a goal of the clinical trial is identified, step **102**. Next, desired evaluability data categories to be collected during the clinical trial are determined, step **104**. Preferably, the desired evaluability data categories pertain to a participant in the clinical trial. Preferably, at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in the trial results.

According to another embodiment of the invention, a method for determining preferred targets for subject compliance is illustrated in FIG. **4**. First, historical subject compliance data and historical protocol data are provided, step **122**. Next, at least one preferred compliance threshold is generated, step **124**. The preferred compliance threshold is preferably generated by quantitative analysis of the historical subject compliance data and the historical protocol data.

According to a further embodiment of the invention, a flow chart illustrating a method of the present invention is set forth in FIG. **5**. First, relevant subject compliance data, and associated protocol data, reflecting subject compliance with research protocols in clinical trials is provided, step **142**. Subject compliance data and associated protocol data is preferably stored in one or more databases **20** and may be gathered from earlier clinical trials and/or earlier activities of a current clinical trial. Optionally, only subject compliance data may be stored, as some applications of the present invention may not require knowledge of associated historical protocol for use of the subject compliance data. For example, analysis of response times to questions may not require knowledge of the maximum permissible time for subjects to answer questions in earlier clinical trials. An output of the present invention preferably includes a database to provide subject compliance data and, preferably, associated protocol data, for later use by the invention.

Next, at least one algorithm representative of the subject compliance data is generated by quantitative analysis of the compliance data, step **144**. Preferably, multiple algorithms are generated. The present invention involves the application of statistical and other quantitative methods to screen existing research data for markers of, e.g. variables related to, non-compliance with research protocols. Preferably, the subject compliance data is also reviewed to exclude invalid data. For example, data reported by one subject that appears to be well outside a range established by all other subjects can indicate invalid data.

Quantitative analysis methods are used to distinguish, identify, and predict instances of good and poor compliance. The quantitative analysis methods of the present invention may include, but are not limited to, application of a variety of statistical and data mining techniques, such as logistic regression, discriminant function analysis, classification and regression trees, neural networks, and multiple linear regression to screen existing data and derive algorithms to identify markers of noncompliance with research protocols.

Once the one or more algorithms of the invention have been derived from analysis of existing data, the algorithms can be translated into specific decision rules, step **146**. Decision rules are essentially reformatted algorithms that can be applied to current subject compliance data to determine whether action is needed, step **148**. Decision rules may determine a threshold of compliance or a threshold of noncompliance. Optionally, a decision rule may identify a spectrum of noncompliance, from minor noncompliance needing only corrective feedback, to significant noncompliance requiring subject removal from the clinical trial. Decision rules may be based on the specific dependent variable used to derive the algorithm or may be based on one or more differing variables.

Decision rules may be translated from algorithms that identify patterns of non-compliance data that are harbingers or leading indicators of later, more serious, non-compliance. This would allow early action to be taken based on these indicators. Such decision rules would typically be in the form of contingencies or conditions based on early compliance indicators.

Optionally, translation of algorithms to decision rules may involve human input or additional factors. For example, balancing the impact of a decision rule against the focus of the clinical trial may result in an alteration of the decision rule. For example, if subjects' heart rates are being monitored, frequency of prompting or loudness of reminder alerts may be minimized so as not to artificially raise subject heart rates. Also, clinical staff may alter decision rules based on their assessment of external factors outside of the scope of the quantitative analysis. An example may include providing more alerts to clinical staff instead of directly to subjects to provide more interaction between clinical staff and the subjects.

A decision rule may also be used to predict which subjects will fail to complete a clinical trial protocol. Therefore, a decision to rule to drop the subject from the clinical trial, or to work to improve subject performance, can be made at an early time. By providing those conducting a clinical trial with early feedback regarding subject noncompliance with a research protocol, the present invention improves clinical trial data

quality and may potentially save both time and money by either improving the compliance of potentially noncompliant subjects or excluding unimprovable noncompliant subjects early in a clinical trial.

If action is determined to be needed, action is prompted, step **150**. Examples of various actions include corrective action, compliance enhancing action, additional prompting of questions, reduced prompting of questions and sending an alert to the clinical staff to discuss an issue with the subject.

Additional detail regarding the method illustrated in FIG. **5** is provided in the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970.

The present invention can yield very high rates of compliance with real-time, real world data collection by subjects. In one embodiment, the present invention for clinical trials (a) builds compliance features and checks into the software that drives the protocol, (b) tracks and optionally gives feedback regarding compliance during the trial, and (c) creates evaluability data that can be used to determine the evaluability of subjects at the end of the trial. Thus, this invention is a systematic methodology for timely, including immediate, data processing, summary, and feedback regarding subject performance in clinical trials.

These examples are meant to be illustrative and not limiting. The present invention has been described by way of example, and modifications and variations of the exemplary embodiments will suggest themselves to skilled artisans in this field without departing from the spirit of the invention. Features and characteristics of the above-described embodiments may be used in combination. The preferred embodiments are merely illustrative and should not be considered restrictive in any way. The scope of the invention is to be measured by the appended claims, rather than the preceding description, and all variations and equivalents that fall within the range of the claims are intended to be embraced therein.

Having described the invention, what is claimed as new and protected by Letters Patent is:

1. A method of determining if action is needed regarding subject compliance during a current clinical trial, wherein said current clinical trial comprises a group of subjects participating in said current clinical trial, comprising the steps of:

providing data on timeliness of a data entry from a previous clinical trial and either a) historical subject compliance data from said previous clinical trial or b) historical protocol data from said previous clinical trial, wherein said historical subject compliance data comprise data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state, and wherein said historical protocol data comprise a question posed to a subject, a frequency of prompting of a subject during a day or week, an amount of time allotted for a subject to respond to a question, or a condition mandating removal of a subject from data analysis or from participation in a clinical trial;

generating a preferred compliance threshold for use during said current clinical trial by quantitative analysis of said data on timeliness of a data entry from said previous clinical trial and either a) said historical subject compliance data from said previous clinical trial or b) said historical protocol data from said previous clinical trial; and

obtaining subject compliance information from a subject in said group of subjects participating in said current clinical trial comprising using a portable electronic device capable of displaying information and receiving and storing input from a user to obtain said subject compliance information from said subject in said group of subjects participating in said current clinical trial; and

comparing said subject compliance information from said subject in said group of subjects participating in said current clinical trial to said preferred compliance threshold to determine if said action is needed for said subject in said group of subjects participating in said current clinical trial, wherein said action comprises removing all or part of data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of the data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial from said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial regarding compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on the compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in the monitoring and correcting of subject compliance.

2. The method of claim **1**, further comprising a step of prompting said action if the step of comparing indicates that said action is needed.

3. The method of claim **1**, wherein said compliance threshold remains unchanged throughout said current clinical trial.

4. A method of prompting an action if subject noncompliance indicates said action is needed during a current clinical trial wherein said current clinical trial comprises a group of subjects participating in said current clinical trial, comprising the steps of:

providing data on timeliness of a data entry and historical subject compliance data from a previous clinical trial, wherein said historical subject compliance data comprise data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state; generating a predictive algorithm for predicting subject noncompliance by quantitative analysis of said historical subject compliance data;

translating said predictive algorithm into at least one prediction rule for use during said current clinical trial;

obtaining subject compliance information from a subject in said group of subjects participating in said current clinical trial comprising using a portable electronic device capable of displaying information and receiving and storing input from a user to obtain said subject compliance information;

comparing said subject compliance information from said subject in said group of subjects participating in said current clinical trial to the at least one prediction rule to

determine if said action is needed for said subject in said group of subjects participating in said current clinical trial; and

prompting said action if the step of comparing indicates that said action is needed.

5. The method of claim **4**, wherein said step of providing further comprises providing historical protocol data from said previous clinical trial and wherein said step of generating further comprises quantitative analysis of said historical protocol data, wherein said historical protocol data comprise a question posed to a subject, a frequency of prompting of a subject during a day or week, an amount of time allotted for a subject to respond to a question, or a condition mandating removal of a subject from data analysis or from participation in a clinical trial.

6. The method of claim **4**, further comprising a step of creating an evaluability database adapted to store data related to subject compliance.

7. The method of claim **6**, further comprising a step of providing access to said evaluability database to a sponsor to allow said sponsor to make a determination regarding said subject in said group of subjects participating in said current clinical trial based on data from said evaluability database.

8. The method of claim **6**, wherein said evaluability database is tailored to a condition affecting said subject in said group of subjects participating in said current clinical trial.

9. The method of claim **4**, wherein said step of providing employs at least one database containing said the historical subject compliance data.

10. The method of claim **4**, wherein said prediction rule is generated without data from activities of said current clinical trial.

11. A method of determining if an action is needed regarding subject compliance during a current clinical trial, wherein said current clinical trial comprise a group of subjects participating in said current clinical trial, comprising the steps of:

providing data on timeliness of a data entry and historical subject compliance data from a previous clinical trial, wherein said historical subject compliance data comprises data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state;

generating an algorithm by quantitative analysis of said data on timeliness of a data entry and said historical subject compliance data;

translating said algorithm into a decision rule for use during said current clinical trial;

obtaining subject compliance information from a subject in said group of subjects participating in said current clinical trial; and

comparing said subject compliance information from said subject in said group of subjects participating in said current clinical trial to said decision rule on a portable electronic device or a computer to determine if said action is needed for said subject in said group of subjects participating in said current clinical trial, wherein said action comprises removing all or part of data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial from said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial regarding compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in monitoring and correcting of subject compliance.

12. The method of claim **11**, wherein said step of providing further comprises providing historical protocol data from said previous clinical trial and wherein said step of generating further comprises quantitative analysis of said historical protocol data, wherein said historical protocol data comprise a question posed to a subject, a frequency of prompting of a subject during a day or week, an amount of time allotted for a subject to respond to a question, or a condition mandating removal of a subject from data analysis or from participation in a clinical trial.

13. The method of claim **11**, further comprising prompting said action if the step of comparing indicates that said action is warranted.

14. The method of claim **1**, wherein said action further comprises reducing a number of occurrences of said step of obtaining subject compliance information.

15. The method of claim **11**, wherein said action further comprises increasing a number of occurrences of said step of obtaining said subject compliance information.

16. The method of claim **11**, wherein said action further comprises giving a reward to said subject in said group of subjects participating in said current clinical trial.

17. The method of claim **11**, wherein said step of obtaining comprises using a portable electronic device capable of displaying information and receiving and storing input from a user.

18. The method of claim **11**, wherein said decision rule is generated without data from activities of said current clinical trial.

19. A computer readable medium suitable for use in an electronic device and having instructions recorded thereon for execution on said electronic device, said instructions comprising the steps of:

providing data on timeliness of a data entry from a previous clinical trial and either a) historical subject compliance data from said previous clinical trial or b) historical protocol data from said previous clinical trial, wherein said historical subject compliance data comprise data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state, and wherein said historical protocol data comprise a question posed to a subject, a frequency of prompting of a subject during a day or week, an amount of time allotted for a subject to respond to a question, or a condition mandating removal of a subject from data analysis or from participation in a clinical trial; and

generating a preferred compliance threshold for use during a current clinical trial by quantitative analysis of said data on timeliness of a data entry from said previous clinical trial and either a) said historical subject compliance data from said previous clinical trial or b) said

historical protocol data from said previous clinical trial, wherein said current clinical trial comprises a group of subjects participating in said current clinical trial,

obtaining subject compliance information from a subject in said group of subjects participating in said current clinical trial, comprising using a portable electronic device capable of displaying information and receiving and storing input from a user to obtain said subject compliance information from said subject in said group of subjects participating in said current clinical trial; and

comparing subject compliance information from said subject in said group of subjects participating in said current clinical trial to said preferred compliance threshold to determine if an action is needed for said subject in said group of subjects participating in said current clinical trial, wherein said action comprises removing all or part of data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial from said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial regarding compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in monitoring and correcting of subject compliance.

20. The computer readable medium of claim **19**, wherein said compliance threshold remains unchanged throughout said current clinical trial.

21. A computer readable medium suitable for use in an electronic device and having instructions recorded thereon for execution on said electronic device, said instructions comprising steps of:

providing data on timeliness of a data entry and historical subject compliance data from a previous clinical trial, wherein said historical subject compliance data comprise data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state;

generating an algorithm reflective of said historical subject compliance data by quantitative analysis of said data on timeliness of a data entry and said historical subject compliance data;

translating said algorithm into at least one decision rule for analyzing subject compliance information during a current clinical trial, wherein said current clinical trial comprises a group of subjects participating in said current clinical trial;

obtaining said subject compliance information from a subject in said group of subjects participating in said current clinical trial;

comparing said subject compliance information from said subject in said group of subjects participating in said current clinical trial to said decision rule to determine if an action is needed for said subject in said group of subjects participating in said current clinical trial; and

prompting said action if the step of comparing indicates that said action is needed for said subject in said group of subjects participating in said current clinical trial, wherein said action comprises removing all or part of data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial from said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial regarding compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in monitoring and correcting of subject compliance.

22. A computer readable medium suitable for use in an electronic device and having instructions recorded thereon for execution on said electronic device, said instructions comprising steps of:

providing data on timeliness of a data entry from said previous clinical trial and either a) historical subject compliance data from said previous clinical trial or b) historical protocol data from said previous clinical trial, wherein said historical subject compliance data comprise data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state, and wherein said historical protocol data comprise a question posed to a subject, a frequency of prompting of a subject during a day or week, an amount of time allotted for a subject to respond to a question, or a condition mandating removal of a subject from data analysis or from participation in a clinical trial;

generating a spectrum of compliance representative of said historical subject compliance data or said historical protocol data by quantitative analysis of said data on timeliness of a data entry and said historical subject compliance data or said historical protocol data;

obtaining subject compliance information from a subject in a group of subjects participating in a current clinical trial, wherein said current clinical trial comprises said group of subjects participating in said current clinical trial;

comparing said subject compliance information from said subject in said group of subjects participating in said current clinical trial to said spectrum of compliance representative to determine if an action is needed for said subject in said group of subjects participating in said current clinical trial; and

prompting said action if said step of comparing indicates that said action is needed for said subject in said group of subjects participating in said current clinical trial,

wherein said action comprises removing all or part of data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial from said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial regarding compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in monitoring and correcting of subject compliance.

23. A computer readable medium suitable for use in an electronic device and having instructions recorded thereon for execution on said electronic device, said instructions comprising steps of:

providing data on timeliness of a data entry and historical subject compliance data from a previous clinical trial, wherein said historical subject compliance data comprise data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state;

generating a predictive algorithm for predicting subject noncompliance by quantitative analysis of said data on timeliness of a data entry and said historical subject compliance data;

translating said predictive algorithm into at least one prediction rule for use during a current clinical trial;

obtaining subject compliance information from a subject in a group of subjects participating in said current clinical trial wherein said current clinical trial comprises said group of subjects participating in said current clinical trial;

comparing said subject compliance information from said subject in said group of subjects participating in said current clinical trial to said prediction rule to determine if an action is needed for said subject in said group of subjects participating in said current clinical trial; and

prompting said action if said step of comparing indicates that said action is needed for said subject in said group of subjects participating in said current clinical trial, wherein said action comprises removing all or part of the data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of the data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial from said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial regarding compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in monitoring and correcting of subject compliance.

24. A computer readable medium suitable for use in an electronic device and having instructions recorded thereon for execution on said electronic device for determining if an action is needed regarding subject compliance during a current clinical trial, wherein said current clinical trial comprises a group of subjects participating in said current clinical trial, said instructions comprising steps of:

providing data on timeliness of a data entry and historical subject compliance data from a previous clinical trial, wherein said historical subject compliance data comprise data on a ratio of completed assessments to expected assessments, data on a subject's compliance with a medication regimen, data on a disease episode, or data on a characteristic of a subject's disease state;

generating an algorithm by quantitative analysis of said data on timeliness of a data entry and said historical subject compliance data;

translating said algorithm into at least one decision rule for use during said current clinical trial;

obtaining subject compliance information from a subject in said group of subjects participating in said current clinical trial; and

comparing said subject compliance information from said subject in said group of subjects participating in said current clinical trial to said decision rule to determine if said action is needed for said subject in said group of subjects participating in said current clinical trial, wherein said action comprises removing all or part of the data from said subject in said group of subjects participating in said current clinical trial from data analysis, removing all or part of the data from said subject in said group of subjects participating in said current clinical trial from a report, removing said subject in said group of subjects participating in said current clinical trial from said current clinical trial, prompting said subject in said group of subjects participating in said current clinical trial to view said portable electronic device, alerting clinical staff to contact said subject in said group of subjects participating in said current clinical trial regarding compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to encourage continued compliance with said current clinical trial, providing compliance feedback to said subject in said group of subjects participating in said current clinical trial to remediate poor compliance with said current clinical trial, providing a report on compliance of said subject in said group of subjects participating in said current clinical trial to said clinical staff or a clinical trial sponsor, or training said clinical staff in monitoring and correcting of subject compliance.

25. The method of claim **1**, wherein said step of providing comprises providing said historical protocol data, and

wherein said step of generating further comprises quantitative analysis of said historical protocol data.

26. The method of claim **1**, **4**, or **11**, wherein said step of generating employs multiple linear regression, discriminant function analysis, logistic regression, neural networks, classification trees or regression trees.

27. The method of claim **1** or **11**, wherein said step of providing employs at least one database containing the historical subject compliance data.

28. The method of claim **1**, **4**, or **11**, wherein said historical subject compliance data further comprise data on whether a subject had a relationship with a doctor or other medical professional, data on a number or percent of prompts not replied to by a subject, data on a subject's sleep/wake cycle, data on whether a subject had a bowel movement, data on an amount of time a portable electronic device is in suspend mode, data on a subject's gender, or data on a subject's location.

29. The method of claim **1**, **4**, or **11**, wherein said action further comprises decreasing said portable electronic device's prompt frequency, increasing said portable electronic device's prompt frequency, or increasing the loudness of an audible prompt of said portable electronic device.

30. The method of claim **1**, **4**, or **11**, wherein said action further comprises administering a reward to said subject in said group of subjects participating in said current clinical trial.

31. The computer readable medium of claim **19**, **21**, **22**, **23**, or **24**, wherein said historical subject compliance data further comprise data on whether a subject had a relationship with a doctor or other medical professional, data on a number or percent of prompts not replied to by a subject, data on a subject's sleep/wake cycle, data on whether a subject had a bowel movement, data on an amount of time a portable electronic device is in suspend mode, data on a subject's gender, or data on a subject's location.

32. The computer readable medium of claim **19**, **21**, **22**, **23**, or **24**, wherein said action further comprises decreasing said portable electronic device's prompt frequency, increasing said portable electronic device's prompt frequency, increasing the loudness of an audible prompt of said portable electronic device, or administering a reward to said subject in said group of subjects participating in said current clinical trial.

33. The computer readable medium of claim **23**, wherein said prediction rule is generated without data from activities of said current clinical trial.

34. The computer readable medium of claim **21** or **24**, wherein said decision rule is generated without data from activities of said current clinical trial.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,065,180 B2
APPLICATION NO. : 09/825533
DATED : November 22, 2011
INVENTOR(S) : Hufford et al.

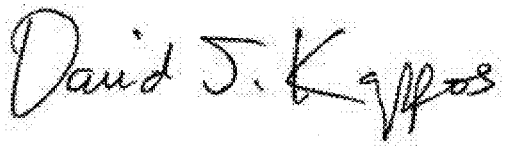
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1593 days.

Signed and Sealed this
Twenty-fourth Day of July, 2012



David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,065,180 B2
APPLICATION NO. : 09/825533
DATED : November 22, 2011
INVENTOR(S) : Michael R. Hufford et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

COLUMN 17, LINE 28, CLAIM 9:

"said the historical" should be --said historical--

Signed and Sealed this
Fourteenth Day of April, 2015

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

US008145519B2

(12) **United States Patent**
Hufford et al.

(10) **Patent No.: US 8,145,519 B2**
(45) **Date of Patent: Mar. 27, 2012**

(54) **SYSTEM FOR CLINICAL TRIAL SUBJECT COMPLIANCE**

(75) Inventors: **Michael Hufford**, San Diego, CA (US); **David Peterson**, Scotts Valley, CA (US); **Jean Paty**, Pittsburgh, PA (US); **Saul Shiffman**, Pittsburgh, PA (US)

(73) Assignee: **invivodata®, Inc.**, Pittsburgh, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/211,133**

(22) Filed: **Aug. 16, 2011**

(65) **Prior Publication Data**

US 2012/0029940 A1 Feb. 2, 2012

Related U.S. Application Data

(63) Continuation of application No. 09/825,533, filed on Apr. 2, 2001, now Pat. No. 8,065,180.

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/11**; 705/3

(58) **Field of Classification Search** 705/2, 3, 705/4, 11

See application file for complete search history.

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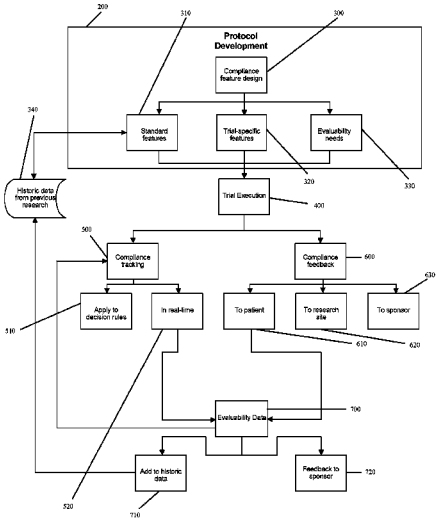
Primary Examiner — Lindsay M. Maguire

(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich & Rosati

(57) **ABSTRACT**

The present invention is designed to develop research protocols for clinical trials. The invention also can track and enhance subject compliance with a research protocol. The invention further provides evaluability data related to subject performance in the clinical trial. According to an alternative embodiment of the invention, a portable electronic device is used to query and collect data from the subject.

63 Claims, 5 Drawing Sheets



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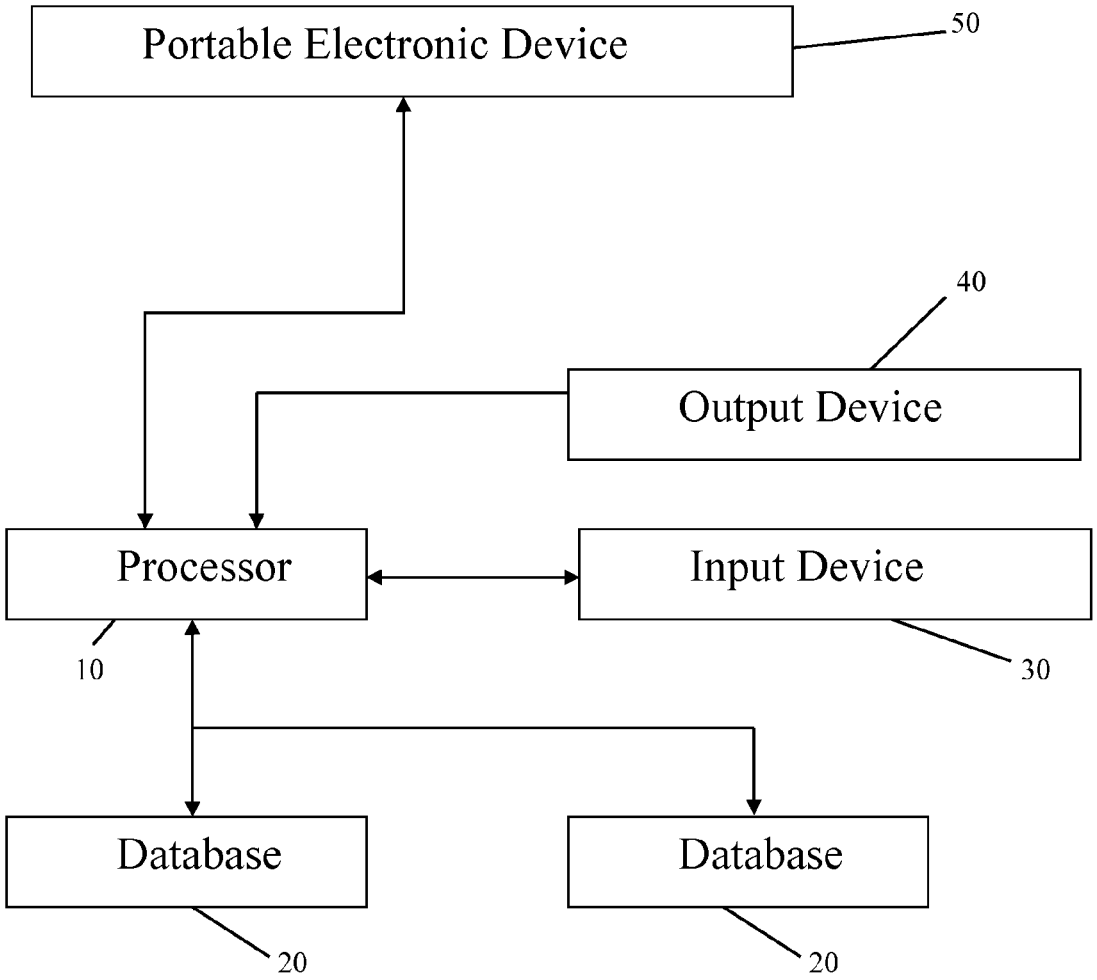
Portable Electronic Device
50
40
Output Device
Processor
Input Device
10
30
Database
Database
20
20

FIGURE 1

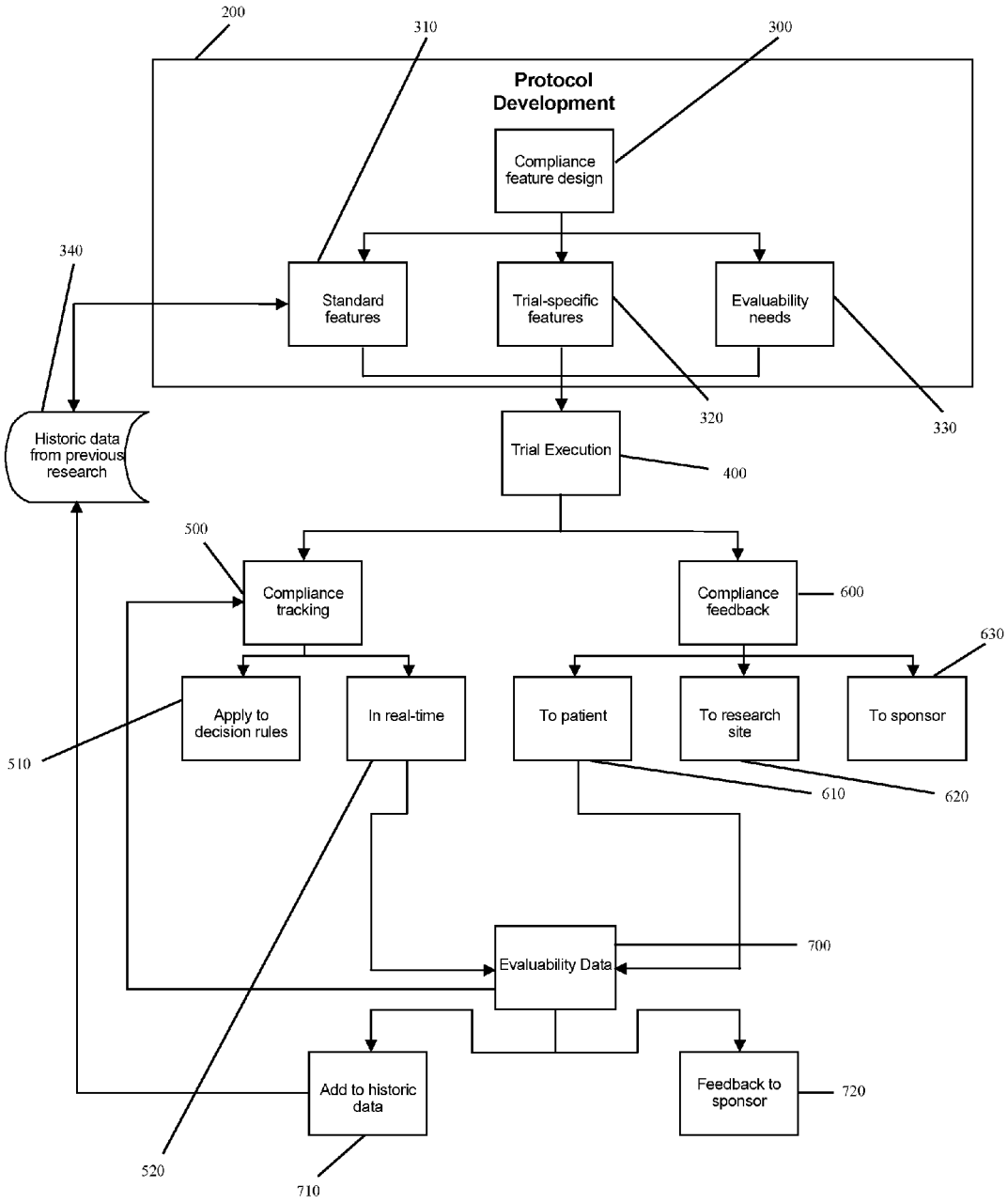
200
310
300
Protocol Development
Compliance feature design
340
Standard features
Trial-specific features
Evaluability needs
320
330
Historic data from previous research
Trial Execution
400
500
Compliance tracking
Compliance feedback
600
630
Apply to decision rules
In real-time
To patient
To research site
To sponsor
510
610
620
700
Evaluability Data
Add to historic data
Feedback to sponsor
720
520
710

FIGURE 2

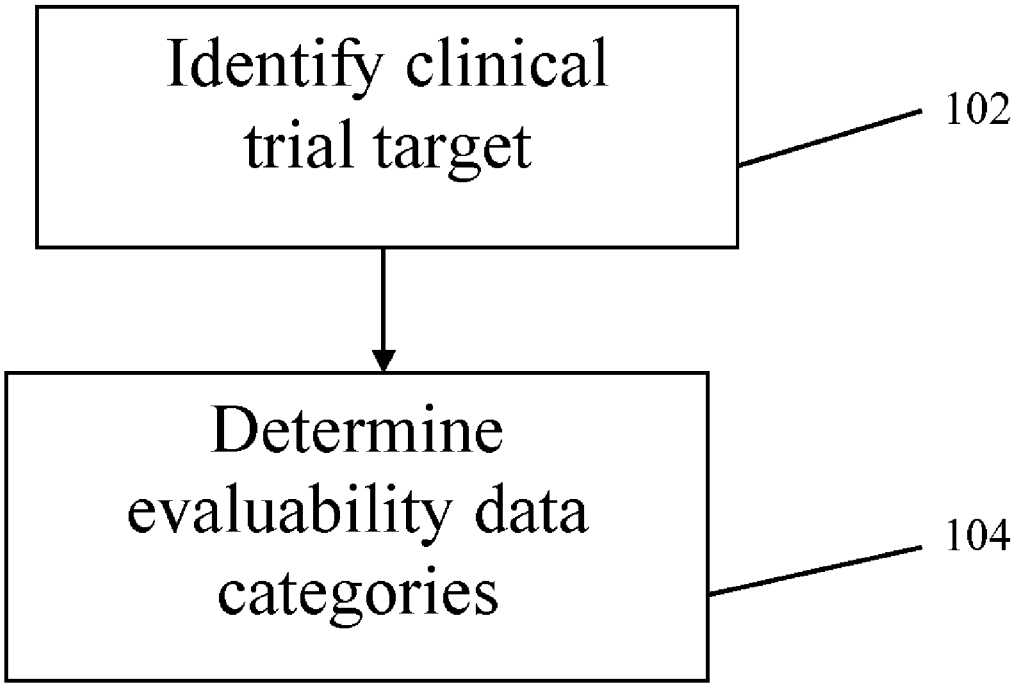
Identify clinical trial target
102
Determine evaluability data categories
104

FIGURE 3

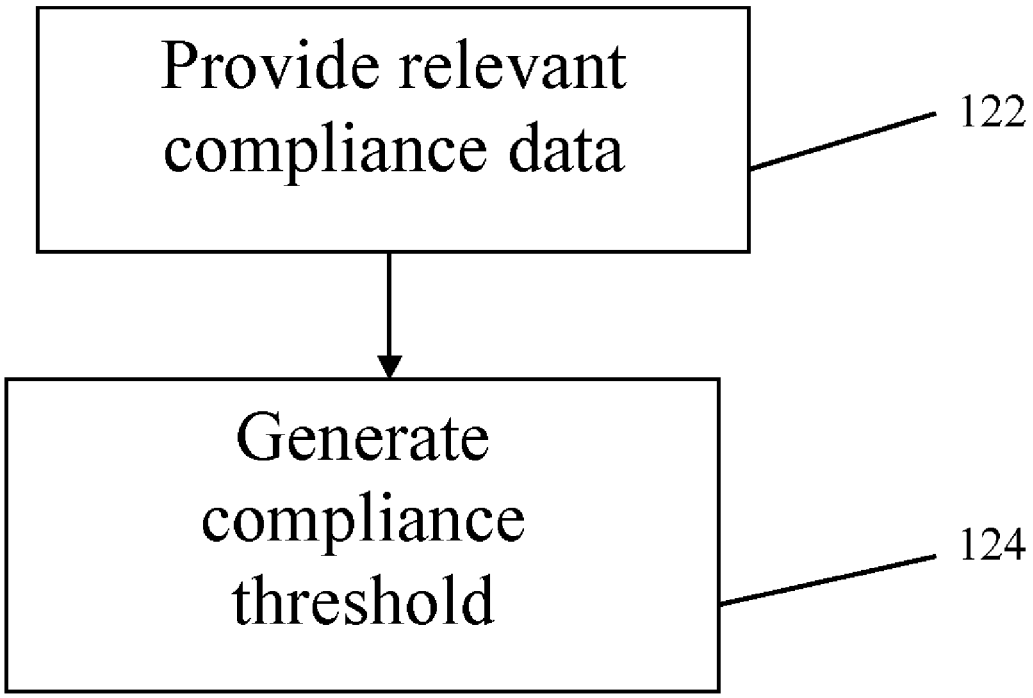
Provide relevant compliance data
122
Generate compliance threshold
124

FIGURE 4

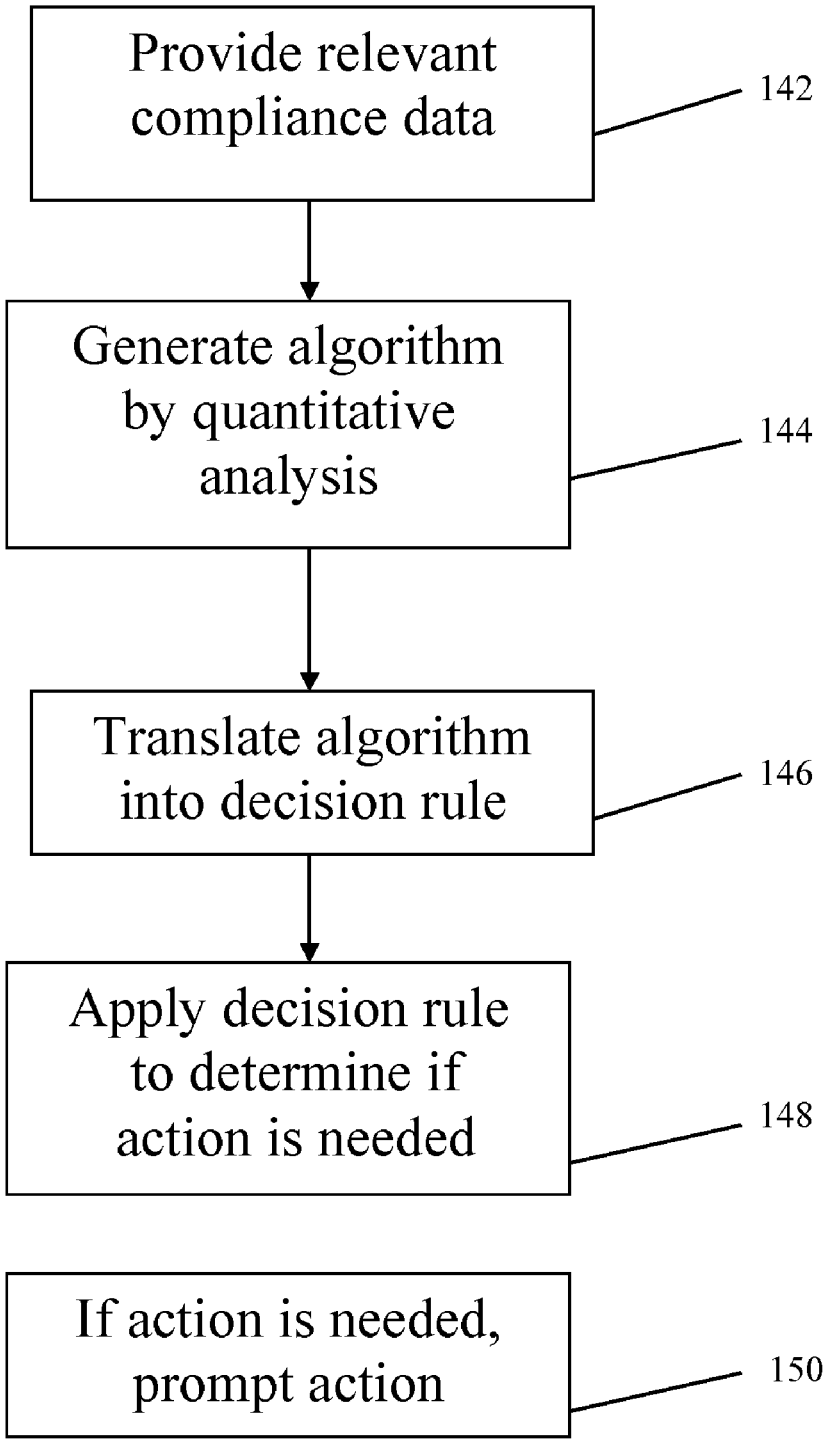
Provide relevant compliance data
142
Generate algorithm by quantitative analysis
144
Translate algorithm into decision rule
146
Apply decision rule to determine if action is needed
148
If action is needed, prompt action
150

FIGURE 5

SYSTEM FOR CLINICAL TRIAL SUBJECT COMPLIANCE

REFERENCE TO RELATED APPLICATIONS

This application is a continuation patent application of U.S. Utility application Ser. No. 09/825,533, filed Apr. 2, 2001, now U.S. Pat. No. 8,065,180; the subject matter of this application relates to the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970, also filed on Apr. 2, 2001; the aforementioned applications, and the references cited therein, are incorporated herein by reference in their entirety.

FIELD OF INVENTION

The present invention relates to conducting clinical trials. Specifically, the invention relates to research protocol development, management of subject behavior and distribution of evaluability data.

BACKGROUND OF THE INVENTION

Noncompliance with research protocols can be especially problematic, potentially resulting in unusable trial data. Typically, subjects are given a paper-based diary and asked to make scheduled entries regarding their illness, medication effects, as well as other data entries recording events as they happen. Subjects must keep track of the time of day, where they are in the sequence of events for any given day, and the appropriate procedures they are to follow across days. Many subjects do not complete their diaries or complete their diaries long after the events that are to be logged. Eight studies have examined compliance rates of these paper diaries by covertly collecting data about the timeliness of entries. A dramatic difference between subjects' reported versus actual compliance was observed. Whereas the paper diaries appeared to indicate high rates of compliance (88%), the actual rates of compliance were significantly lower (54%).

Evaluation of subject compliance with research protocols is often performed by examining only one variable at a time. Such evaluation is not empirically derived by quantitative analysis of existing datasets. Instead the evaluation relies on the researcher's judgment and biases to determine whether and what type of corrective action is required. Furthermore, evaluation of subject compliance with clinical trial protocols has typically not taken into account the domain of the clinical trial or the characteristics of the subjects.

SUMMARY OF THE INVENTION

The goal of clinical trials is to collect valid, reliable data on one or more conditions within a clinical trial group of subjects. Subjects in clinical trials are assigned tasks related to treatment and data collection in accordance with a research protocol. The integrity of clinical trials rests upon subjects' faithful performance of these tasks. If subjects fail to comply with the protocol, the trial will fail to yield reliable, valid trial data or results. Thus, subject noncompliance in clinical trials is a significant risk and cost to the pharmaceutical industry. Accordingly, the creation of appropriate research protocol, management and enhancement of subject behavior and effective distribution of clinical trial data is of substantial value to clinical research.

The benefits of a system that can track and enhance subject compliance in a clinical trial include: reliable, valid data; increased statistical power, reduced clinical trial costs through smaller sample sizes; reduced time to complete the clinical trial; and, ultimately, reduced time to get a drug or medical device to market.

According to one embodiment of the invention, a method of protocol development for a clinical trial is provided. The method includes the steps of identifying a clinical trial target reflecting a goal of the clinical trial, determining desired evaluability data categories to be gathered pertaining to a participant in the clinical trial, wherein an evaluability data of at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in one or more of the trial results.

According to another embodiment of the invention, a method of determining preferred targets for subject compliance is provided, having the steps of providing at least one of the group of historical subject compliance data and historical protocol data and generating at least one preferred compliance threshold by quantitative analysis of at least one of the group of the historical subject compliance data and the historical protocol data.

Another embodiment of the invention provides a method of monitoring subject compliance and having the steps of providing historical subject compliance data, generating at least one algorithm reflective of the historical subject compliance by quantitative analysis of the historical subject compliance data and the historical protocol data, translating the at least one algorithm into at least one decision rule for analyzing subject compliance information, obtaining the subject compliance information, comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a method of determining subject compliance and having the steps of providing historical subject compliance data and historical protocol data, generating a spectrum of compliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data, obtaining subject compliance information, comparing the spectrum of compliance to the subject compliance information to determine if corrective action is needed, and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a method of predicting subject noncompliance and having the steps of providing historical subject compliance data, generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance data, translating the at least one predictive algorithm into at least one prediction rule, obtaining subject compliance information, comparing the subject compliance information to the at least one prediction rule to determine if action is needed, and prompting action if the step of comparing indicates that action is needed.

A further embodiment of the invention provides a method of enhancing subject compliance and having the steps of providing historical subject compliance data, generating at least one algorithm by quantitative analysis of the historical subject compliance data, translating at least one algorithm into at least one decision rule, obtaining subject compliance

information and comparing the subject compliance information to the at least one decision rule to determine if affirmative action is warranted.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a user and an alarm electrically coupled to the portable electronic device and having varying alarm tones, wherein the varying alarm tones are emitted by the alarm if the user does not comply with a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a user and an alarm electrically coupled to the portable electronic device and having a tactile alarm.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device examines the input and reviews the input for inconsistencies.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device increases an amount of prompting of the input from the participant upon an automated determination that the participant does not comply with a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device decreases an amount of prompting of the input from the participant upon an automated determination that the participant has reported a predetermined number of events other than in response to the prompting by the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a user, wherein the user is provided feedback based on the determination of whether the user has followed a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of identifying a clinical trial target reflecting a goal of the clinical trial, determining desired evaluability data categories to be gathered pertaining to a participant in the clinical trial, wherein an evaluability data of at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in at least one result of the clinical trial.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing at least one of the group of historical subject compliance data and historical protocol data and generating at least one preferred compliance threshold by quantitative analysis of at least one of the group of the historical subject compliance data and the historical protocol data.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one algorithm reflective of the historical subject compliance data by quantitative analysis of the historical subject compliance data, translating the at least one algorithm into at least one decision rule for analyzing subject compliance information and obtaining the subject compliance information. The steps further include comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data and historical protocol data, generating a spectrum of compliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data, obtaining subject compliance information, comparing the spectrum of compliance to the subject compliance information to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance data, translating the at least one predictive algorithm into at least one prediction rule, obtaining subject compliance information, comparing the subject compliance information to the at least one prediction rule to determine if action is needed and prompting action if the step of comparing indicates that action is needed.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one algorithm by quantitative analysis of the historical subject compliance data, translating the at least one algorithm into at least one decision rule and obtaining subject compliance information and comparing the subject compliance information to the at least one decision rule to determine if affirmative action is warranted.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of displaying information to the participant and prompting input from the participant, accepting the input from the participant and decreasing an amount of prompting of the input from the participant upon an upon an automated determination that the participant has reported a predetermined number of events other than in response to the prompting by the portable electronic device.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following description and apparent from the accompanying drawings.

FIG. **1** illustrates a system according to an embodiment of the present invention;

FIG. **2** provides a functional layout of one embodiment of the present invention;

FIG. **3** illustrates a method according to an embodiment of the present invention;

FIG. **4** illustrates a method according to an embodiment of the present invention; and

FIG. **5** illustrates a method according to an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The illustrative embodiment of the present invention is designed to develop research protocols for clinical trials, track and enhance subject compliance with protocol requirements and provide evaluability data related to subject performance in the clinical trial.

The illustrative embodiment involves an empirically derived set of algorithms and decision rules to predict, track and enhance subject compliance with research protocols. The illustrative embodiment uses algorithms and decision rules to provide an empirical approach for analysis of different types of subject noncompliance with research protocols. This actuarial approach to predicting and managing subject noncompliance with clinical trial protocols is consistent with empirical research demonstrating the superiority of actuarial prediction of human behavior as compared to subjective clinical judgment. According to an alternative embodiment of the invention, a portable electronic device is used to query and collect data from the subject.

As used herein "clinical trial" refers to a broad range of data collecting activities, including studies directed to monitoring of one or more conditions within a clinical trial group of subjects. One such example includes drug trials involving humans. As used herein "subject" refers to any participant in a clinical trial, whether or not the subject has any relationship to a doctor or other medical professional.

Data "evaluability" refers to the usefulness of the data for the intended clinical trial purpose. Various factors may affect data evaluability, principally the circumstances under which the data was collected and how closely the circumstances with the research protocol for the specific clinical trial.

"Trial data" or "clinical trial data" refers to data gathered for the principle purpose of the clinical trial. For example, trial data would include pain levels experienced by subjects in a pain medication clinical trial or craving levels in an anti-smoking medication clinical trial.

"Evaluability data" or "compliance data" or "compliance information" is data that relates to the circumstances under which the trial data was collected or other data pertaining to characteristics of the trial data or other evaluability data. Some examples include timeliness, consistency with other collected data, proximity of the data to an expected data range and completeness of the data.

"Historical protocol data" includes data specifying the research protocol of earlier clinical trials. Examples of historical protocol data can include questions posed to subjects, frequency of prompting of a subject during various times of the day or week, time allowed for subjects to respond to questions, requirements of subject behavior, and conditions mandating removal of a subject from specific analyses or from participation in the clinical trial.

As used herein "portable electronic device" refers to any electronic device that can be adapted for use by a subject and/or clinical staff for viewing and/or inputting information. Preferably, the portable electronic device will also have a visual, audible or tactile alarm to gain the attention of the subject. For example, a pager having a vibration alarm may be used as a portable electronic device. Further examples include, pagers with audible alarms and/or text messaging capabilities, a laptop computer or a cell phone. Preferably, according to the invention, a portable electronic device will be a handheld computer provided with a display and a data input feature, such as a touch-sensitive screen, or buttons to enable a subject to respond to questions posed on the display or to input unsolicited information. Examples of such portable electronic devices include the Palm Pilot by Palm, Inc or Windows-based devices running Pocket PC from Microsoft Corporation. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem and/or a network, such as a LAN or the Internet.

According to an embodiment of the present invention, a system is provided as shown in FIG. **1**. A processor **10** is provided and is adapted to communicate with at least one database **20**. As discussed below, the database preferably stores data related to subject compliance and associated research protocols. An input device **30** is also provided to allow the subject or another person to provide input to the processor **10**. The input device **30** may be a keyboard, a modem or other such device adapted for communication with the processor. An output device **40** is also preferably provided to receive and display information from the processor **10**. Examples of output devices **40** include a printer and a monitor.

In one embodiment of the invention, a portable electronic device **50** is provided and selectively operatively coupled to the processor **10**. The portable electronic device **50** can also include a processor and may serve as an alarm, an input device, an output device, and/or a database.

In one embodiment, the present invention includes software that resides on a portable electronic device. Preferably, the portable electronic device is a handheld portable computer.

In another embodiment, the present invention includes software that resides on a server. Optionally, the server may communicate with a computer or portable electronic device.

FIG. **2** provides a functional layout of an embodiment of the present invention. Protocol development **200** involves a review of the goals of the clinical trial to determine research protocol including subject compliance targets prior to the start of the clinical trial. Preferably, compliance targets are developed in accordance with the invention disclosed in the co-pending patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research". Optionally, protocol development **200** can involve analysis of and updates to the protocol while the clinical trial is underway. Therefore, in accordance with an optional embodiment of the present invention, protocol development **200** can occur during trial execution **400**.

The present invention preferably involves identification of compliance targets relevant to specific features of the research protocol prior to the start of the clinical trial. These compliance targets can then be used to track subject compliance. Once these compliance targets have been identified, compliance-enhancing features can optionally be developed for a specific clinical trial and can preferably be incorporated into the functionality of the portable electronic device.

It is also within the scope of the present invention to use empirically derived algorithms to determine the best compliance targets for a specific clinical trial by the use of the quantitative analysis methods of the patent application titled

"Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research". These algorithms could identify non-intuitive, combinations of variables derived from historical data from previous clinical trials. Combinations of different compliance targets identified from other clinical trials could be used to predict a set of variables to be tracked in order to maximize an ability to detect subject noncompliance. Preferably, algorithms are translated to decision rules to ease detection of subject noncompliance.

Examples of various types of data that may be collected according to an embodiment of the invention include variables that may represent 'non-intuitive' predictors such as: gender of the subject, disease severity, the time of the year, and the day of the week.

Protocol development **200** preferably includes compliance feature design **300** to incorporate features into the research protocol to enhance subject performance in complying with the research protocol. Compliance features are preferably active during the execution of the clinical trial. Compliance features may be provided by a portable electronic device driving the protocol for subjects by guiding the subject through the protocol, not requiring the subject to remember the details of all the research protocol. For example, the portable electronic device can activate an alarm to prompt the subject to view the device. The portable electronic device can then prompt the subject to answer appropriate questions to gather information as specified by the research protocol. Optionally, the portable electronic device can modify and tailor questions based on information provided by the subject or based on input from the clinical staff. Preferably, each subject is provided with a portable electronic device and will keep the portable electronic device in their possession at all times during the clinical trial.

By the use of the portable electronic device, the present invention also allows subjects to administer self-reports of trial data including subjective reports, such as pain reduction, objective symptom reporting, such as bowel movement or asthmatic episode and cognitive measures, such as arithmetic tasks or reaction time. The electronic device may also optionally be configured to synchronize with any portable physiological measurement device to gather data from, or communicate with, the physiological device.

Moreover, portable electronic devices can optionally track all aspects of their use, resulting in a comprehensive record of subject compliance with the research protocol. A preferred embodiment of the invention allows clinical trial staff to systematically collect data regarding subject compliance by tracking a variety of different components of compliance, as well as check in compliance against empirically derived algorithms and decision rules of compliance. These empirically derived algorithms and decision rules allow the disclosed invention to examine the data for nonintuitive and complex combinations of predictors to proactively determine whether the observed pattern of interaction with the portable electronic device suggests noncompliance. The patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", provides additional detail regarding such algorithms and decision rules.

The portable electronic device also preferably conducts ongoing compliance checks and gives the subject feedback about their performance. For example logical psychometric or other inconsistencies can be determined by the portable electronic device. Actions of the portable electronic device are preferably processed according to decision rules. The portable electronic device can also vary its behavior based on the subject's behavior. For example, prompt frequency may be delayed or increased, or louder prompts may be provided. Also, vibration or visual alerts can be generated. Evaluability data related to the activity conducted with a portable electronic device is preferably transferred from the portable electronic device to a database for collecting information from multiple portable electronic devices. Such a database is preferably, a database hosted at a central location. In one embodiment of the invention, the database is hosted on PC-based server software and is preferably adapted for communication with other computers. Additional compliance checks are preferably performed on the server and feedback is given to subjects by clinical trial staff; the feedback could be face-to-face or remote. Finally, the evaluability data is used to determine the evaluability of subject data, and screen out subjects or parts of subjects' data during the data analysis and reporting of the clinical trial data or results. Thus, the present invention is preferably utilized from beginning to end of a clinical trial.

Compliance feature design **300** includes standard features **310**, trial specific features **320**, and evaluability needs **330**. Incorporating standard features **310** within the research protocol preferably involves review of historic data from previous research **340**, including prior operations of the invention on earlier clinical trials and other sources of data involving subject compliance and, preferably, associated research protocols. Preferably, standard features **310** incorporated into the protocol will be derived in accordance with co-pending patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", and will involve historic data from related clinical trials. For example, a clinical trial related to a cardiovascular condition will preferably develop standard compliance features **310** from historic data involving cardiovascular clinical trials.

Many types of compliance enhancing features are possible. For example, to enhance subject compliance with regular monitoring of symptom severity, varying alarm tones could be used to engender compliance. For example, if subjects are prompted using an audible 'beep' to complete a symptom report, the tone may increase in volume and/or pitch to increase the probability that subjects will complete the report. Other examples of compliance-enhancing features include allowing subjects to delay a report if they are busy. Subjects can also initiate a brief suspension of monitoring if their activity precludes completion of a report, for example, while driving. The portable electronic device could automatically re-initiate monitoring after a set amount of time has elapsed, or alternatively the subject could re-initiate monitoring. These examples do not represent an exhaustive list of compliance enhancing features of the present invention.

According to a preferred embodiment of the present invention, the following data is gathered by the use of a portable electronic device: the number of completed assessments or the ratio to expected assessments; the number or percent of prompts from the portable electronic device for data input that were not replied to by the subject; a variety of time based variables, such as for example, a sleep/wake cycle, obtained by having the portable electronic device record when subjects went to sleep and awoke each day of the clinical trial; the amount of time a subject puts the portable electronic device in a suspend mode that temporarily prevents the diary from prompting the subject for a reply; how often and for how long subjects respond to a prompt by requesting the portable electronic device delay a reply period; the frequency with which a subject abandons the portable electronic device, for example, how often does the subject's pattern of inactivity with the portable electronic device suggest he/she has ceased complying with the research protocol.

Trial specific features **320** may also be included in compliance feature design **300** and may include specific aspects related to the current clinical trial. For example, compliance targets can also be identified based on specific characteristics of the disease state or clinical judgment of the clinical staff. For example, if subjects typically report a certain number of disease episodes per day, the present invention may target episodes per day as one variable to be tracked during the clinical trial and will automatically prompt subjects if a disease episode is not reported every 5 hours.

Evaluability needs **330** may also be incorporated in compliance feature design **300** and may involve tailoring compliance features in order to maximize evaluability data or address specific sponsor requirements. Preferably, evaluability needs **330** will be an integral part of the initial design of the research protocol. An example of an evaluability need **330** is a requirement that subject must report at least 5 disease episodes per day to be included in a particular analysis. In this example, how many disease episodes reports each day may be identified as an important variable to be tracked during trial execution.

During and/or after trial execution **400**, compliance tracking **500** is performed and involves analyzing subject behavior data and comparing it to the research protocol. Compliance tracking data, e.g. evaluability data, is gathered during the clinical trial and compared to historic norms **510** during or after the clinical by the use of decision rules. Additional detail is provided in the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research".

According to a further embodiment of the invention, algorithms can be used with decision rules to automatically generate feedback to both subjects and research staff. For example, an algorithm predicting a pattern of intermittent noncompliance with one facet of a clinical trial protocol could trigger a prompt to the subject on the portable electronic device to remain vigilant. Feedback could also be generated to the research staff to address an issue with the subject. Because the algorithms and decisions are preferably based on formal, empirical, and quantitative criteria, subjectivity can be removed from these decisions, which in turn minimizes the potential for bias.

An embodiment of the present invention preferably tracks compliance with the research protocol expected of subjects, such as timely completion of reports and compliance with the medication regimen. To successfully assess and remediate subject performance in clinical trials, the present embodiment preferably tracks compliance at several levels. If a portable electronic device is used for data entry, compliance may be tracked at the moment of data entry by determining whether or not the entry falls within acceptable parameters of the protocol. For example, is a response to a prompt required to be completed in the morning timely, or is the response delayed until the afternoon. Compliance tracking can also examine the content of the data entry itself to determine whether or not the subject is being compliant with the research protocol. For example: inconsistencies among two or more responses given; subject claiming they are in their living room and swimming. Compliance tracking can also take place over some span of time, such as for example, weekly, to examine patterns or rates of noncompliance over time. Compliance tracking can also be performed against data pertaining to the subject's behavior during the clinical trial. For example, trends in subject response times or in the responses themselves can be determined.

The present invention can optionally reduce the burden on a non-compliant subject in order to increase compliance rates by providing fewer prompts for information. Also, the present invention can reduce the number of prompts for a subject that has provided voluntary, unprompted information. In summary, the present invention can be interactive. The present invention is preferably configured to initially enhance compliance while evaluating compliance as the clinical trial progresses. Preferably, the present invention dynamically adjusts in response to the subject's behavior, in accordance with the decision rules.

Compliance feedback **600** may involve forwarding messages, activating alerts or taking some other action in order to provide information to the subject **610**, the clinical trial staff, including the research site **620**, or to the sponsor **630**. Such messages may be include, for example positive feedback, corrective feedback or a recommendation to dismiss a subject from the clinical trial.

To increase the benefit of the compliance tracking feature of the present invention, compliance feedback is preferably provided to subjects, the research site, and the clinical trial sponsor in a timely fashion. Compliance tracking and compliance feedback may be conducted in an ongoing, timely manner on the portable electronic device itself. Compliance tracking and compliance feedback can occur also occur later, after data has been transmitted to a database, such as a database on a central server. In such a case, compliance feedback instructions can be sent back to the portable electronic device to provide feedback to subjects. Feedback for subjects can optionally be directed to clinical trial staff for delivery to the subjects.

According to an embodiment of the invention, a portable electronic device or a computer, such as a workstation or a server, can automatically check incoming data against a decision rule to determine if the pattern of responses require that a compliance alarm be triggered. Optionally, other demographic variables can also be checked by a decision rule. If one or more decision rules note that a problematic pattern of noncompliance or potential noncompliance is being observed, a number of actions may be taken. Examples of such actions include: posting a message on a website to be reviewed by the sponsor or research site, sending an e-mail or other type of notification, such as an automated call, to the subjects or research site coordinator, instructing the portable electronic device to display a certain message to the subject, instructing the portable electronic device to call the site during the subject's next interaction with the device, etc. These checks can either be triggered manually or automatically upon receipt of the data from the field.

According to an embodiment of the invention, the computer can perform the compliance analyses of incoming data instead of the compliance analyses being conducted by the portable electronic device. For example, the computer can analyze incoming data and compute the ratio of missed to completed assessments. This would be appropriate if the method of collection of the data did not otherwise allow the compliance data to be generated. For example, such a method of collection may involve written forms or an instrumented device not capable of computations.

According to another embodiment of the invention, the computer can execute more extensive compliance analyses than are capable on a portable electronic device. For example, more memory or processing power may be required to use the item response theory to examine the probability that a series of responses are likely as compared to an existing database of population norms for a given measure.

According to a further embodiment of the invention, the computer can aggregate a series of assessment data over time within or between subjects. These aggregated compliance

analyses on the computer allow for greater capacity than may be capable on a portable electronic device.

According to an embodiment of the invention, the computer can provide data to be displayed. Data may be displayed at the computer itself or be transmitted to another location, such as via hardwired or wireless access to the computer, including a LAN or the Internet. The data can be processed to provide a graphical display to interested parties. Examples of those who may be interested in viewing the graphical representation of the compliance data include a site coordinator (who may be interacting with the subject), a clinical research organization (who may be responsible for study execution across a number of research locations), other agencies interested in the collection of the data, or the sponsor of the research.

According to another embodiment of the invention, the computer can provide ongoing aggregation of data across subjects to speed the time required to combine, clean, and make available final data.

The various features of the computer, such as a workstation or server, of the above embodiments of the invention may be used individually or in combination.

Subject changes in behavior in response to compliance feedback may also be assessed. That is, an embodiment of the present invention may assess subjects' behavior in response to feedback regarding their compliance with the research protocol. For example, the software can detect whether or not subjects have begun to follow the research protocol more closely as a function of having received previous feedback about their noncompliance with the protocol.

Compliance feedback can take many forms. Compliance feedback can be given to a subject at varying intervals at any location, ranging from frequent, timely feedback, to more episodic feedback based on aggregate measures of compliance. Systematic compliance feedback may be given to subjects to encourage continued compliance, remediate poor compliance, or administer rewards to subjects for their performance.

Compliance feedback may be given to the clinical trial staff. To maximize the impact of the compliance system on trial success, clinical trial staff preferably receives training in the monitoring and correcting of subject compliance according to the present invention.

In one embodiment, the present invention creates customized graphical summaries of compliance tracking data and produces standardized reports for delivery of compliance feedback to subjects, the research site and/or clinical trail staff. Research sites are instructed on how to give standardized feedback to subjects in order to remediate poor subject compliance.

The aggregation of this compliance feedback can optionally be compiled into subject and clinical trial status reports during the clinical trial. These reports are for the research site and/or sponsors, to be used in evaluating the progress of the clinical trial. These reports contain a summary of subjects' compliance with research protocol, and therefore are an indicator of data evaluability.

Compliance tracking data is timely **520** forwarded as it is collected to an evaluability database **700**. Aggregation of compliance data enhances evaluation of subjects, prompting methodologies and research sites. Aggregated compliance data also allows for subjects to be examined for evaluability analyses. Also, evaluability data may be incorporated in compliance tracking **500** decisions during the course of a clinical trial. The evaluability database **700** also can provide additional historic data **710** to be included in a historic data database **340** upon which further research protocols are developed, as appropriate. The evaluability database **700** is also preferably made available to clinical staff and research sponsors. By making the evaluability database **700** accessible to clinical trial sponsors, sponsors are able to participate in decision making regarding the management of the clinical trial as the clinical trial is conducted. Furthermore, sponsors are able to monitor the progress of a clinical trial as it proceeds.

Evaluability data can be gathered in an evaluability database: a database that contains information relevant to the evaluability or acceptability of data from each subject. Evaluability data represents data that is of significant benefit for clinical trial sponsors. The evaluability database allows clinical trial sponsors to have timely evaluability data regarding the quality and consistency of the trial data. An example of trial data is efficacy data on the impact of the drug or medical device on the subject. In other words, the evaluability data allows clinical trial sponsors to have data about the quality of the trial data.

One specific use of the evaluability database is to determine whether or not a specific subject's data would be used in an analysis. For example, an analysis may be limited to those subjects who met minimal criteria for compliance. Another specific use of the evaluability database is to determine desirable trial data for a specific subject or among multiple subjects. This use of evaluability data involves whether or not specific data points within one or more subjects' trial data would be used in an analysis. For example, among all subjects, only trial data from days when compliance met acceptance criteria may be desired. In each instance, the evaluability data becomes an important and unique source of information regarding trial data quality in a clinical trial.

Evaluability data can be aggregated to create global, as well as disease and population-specific databases. The result of this aggregation of evaluability data provides an ability to predict subject noncompliance in clinical trials. This prediction ability increases as more evaluability data is available.

Evaluability data may also be reviewed by clinical trial staff. The periodicity of the data review could range from weekly to instantaneous, optionally using wireless technology or a web site located on the Internet. During the data review, the data can be checked using algorithms or decision rules to determine whether the pattern of subject behavior up to that point in the clinical trial triggers a decision rule, which may therefore recommend a course of action. Courses of action may include, for example providing feedback to the subject, the research site, the sponsor and/or the clinical trial staff The review may examine data over varying time intervals to determine whether some type of corrective action is necessary. By the use of the present invention, evaluability data can be reviewed for critical patterns of factors related to noncompliance or other events, such as effectiveness of compliance enhancement measures, ranging from within-day assessments to patterns extending over many months of monitoring.

The portable electronic device is also preferably adapted to communicate with another computer to allow the clinical staff to consolidate the data from all subjects in the clinical trial into one location for review or processing. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem and/or a network, such as a LAN or the Internet. For example, by the use of the Internet or a dial-up modem connection, a subject may submit information from the portable electronic device to the clinical staff from the subject's home.

In another embodiment, a portable electronic device or a computer is adapted to communicate with clinical trial equipment used for measuring, monitoring, controlling or recording data or a process of the clinical trial. Examples of such processes include administration of medication or monitoring of heart rates. The portable electronic device or a computer preferably automatically records desired data for incorporation in the clinical trial data or compliance data. A further example of clinical trial equipment is an instrumented bottle cap, which is capable of recording and/or reporting when a bottle is opened or closed.

In another embodiment, clock synchronization can be used to synchronize data from clinical trial equipment used for measuring, monitoring, controlling or recording data or a process of the clinical trial with data collected by a computer or portable electronic device for later analysis.

In another embodiment of the invention, a paper form, such as a case report form, can be used by the subject to record data. The data can then be entered into a database by the use of a portable electronic device or other computer at an appropriate time. Examples of case report forms include hand-written forms and forms that allow for machine readable marks to be made, enabling automated scanning of the case report forms during entry of the data into a computer.

In an alternative embodiment of the present invention, the methods of the present invention may be incorporated in instructions recorded on a medium suitable for use in an electronic device, such as a computer, computer network server or a portable electronic device. The medium can include, for example, a hard disk, RAM medium, diskette, CD-ROM or other optical or magnetic storage medium. The instructions can optionally be stored on a server that can be remote from the subject and/or clinical staff member.

According to a further embodiment of the invention, a flow chart illustrating a method of protocol development of the present invention is set forth in FIG. **3**. First, a clinical trial target reflecting a goal of the clinical trial is identified, step **102**. Next, desired evaluability data categories to be collected during the clinical trial are determined, step **104**. Preferably, the desired evaluability data categories pertain to a participant in the clinical trial. Preferably, at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in the trial results.

According to another embodiment of the invention, a method for determining preferred targets for subject compliance is illustrated in FIG. **4**. First, historical subject compliance data and historical protocol data are provided, step **122**. Next, at least one preferred compliance threshold is generated, step **124**. The preferred compliance threshold is preferably generated by quantitative analysis of the historical subject compliance data and the historical protocol data.

According to a further embodiment of the invention, a flow chart illustrating a method of the present invention is set forth in FIG. **5**. First, relevant subject compliance data, and associated protocol data, reflecting subject compliance with research protocols in clinical trials is provided, step **142**. Subject compliance data and associated protocol data is preferably stored in one or more databases **20** and may be gathered from earlier clinical trials and/or earlier activities of a current clinical trial. Optionally, only subject compliance data may be stored, as some applications of the present invention may not require knowledge of associated historical protocol for use of the subject compliance data. For example, analysis of response times to questions may not require knowledge of the maximum permissible time for subjects to answer questions in earlier clinical trials. An output of the present invention preferably includes a database to provide subject compliance data and, preferably, associated protocol data, for later use by the invention.

Next, at least one algorithm representative of the subject compliance data is generated by quantitative analysis of the compliance data, step **144**. Preferably, multiple algorithms are generated. The present invention involves the application of statistical and other quantitative methods to screen existing research data for markers of, e.g. variables related to, non-compliance with research protocols. Preferably, the subject compliance data is also reviewed to exclude invalid data. For example, data reported by one subject that appears to be well outside a range established by all other subjects can indicate invalid data.

Quantitative analysis methods are used to distinguish, identify, and predict instances of good and poor compliance. The quantitative analysis methods of the present invention may include, but are not limited to, application of a variety of statistical and data mining techniques, such as logistic regression, discriminant function analysis, classification and regression trees, neural networks, and multiple linear regression to screen existing data and derive algorithms to identify markers of noncompliance with research protocols.

Once the one or more algorithms of the invention have been derived from analysis of existing data, the algorithms can be translated into specific decision rules, step **146**. Decision rules are essentially reformatted algorithms that can be applied to current subject compliance data to determine whether action is needed, step **148**. Decision rules may determine a threshold of compliance or a threshold of noncompliance. Optionally, a decision rule may identify a spectrum of noncompliance, from minor noncompliance needing only corrective feedback, to significant noncompliance requiring subject removal from the clinical trial. Decision rules may be based on the specific dependent variable used to derive the algorithm or may be based on one or more differing variables.

Decision rules may be translated from algorithms that identify patterns of non-compliance data that are harbingers or leading indicators of later, more serious, non-compliance. This would allow early action to be taken based on these indicators. Such decision rules would typically be in the form of contingencies or conditions based on early compliance indicators.

Optionally, translation of algorithms to decision rules may involve human input or additional factors. For example, balancing the impact of a decision rule against the focus of the clinical trial may result in an alteration of the decision rule. For example, if subjects' heart rates are being monitored, frequency of prompting or loudness of reminder alerts may be minimized so as not to artificially raise subject heart rates. Also, clinical staff may alter decision rules based on their assessment of external factors outside of the scope of the quantitative analysis. An example may include providing more alerts to clinical staff instead of directly to subjects to provide more interaction between clinical staff and the subjects.

A decision rule may also be used to predict which subjects will fail to complete a clinical trial protocol. Therefore, a decision to rule to drop the subject from the clinical trial, or to work to improve subject performance, can be made at an early time. By providing those conducting a clinical trial with early feedback regarding subject noncompliance with a research protocol, the present invention improves clinical trial data quality and may potentially save both time and money by either improving the compliance of potentially noncompliant subjects or excluding unimprovable noncompliant subjects early in a clinical trial.

If action is determined to be needed, action is prompted, step **150**. Examples of various actions include corrective action, compliance enhancing action, additional prompting of questions, reduced prompting of questions and sending an alert to the clinical staff to discuss an issue with the subject.

Additional detail regarding the method illustrated in FIG. **5** is provided in the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research".

The present invention can yield very high rates of compliance with real-time, real world data collection by subjects. In one embodiment, the present invention for clinical trials (a) builds compliance features and checks into the software that drives the protocol, (b) tracks and optionally gives feedback regarding compliance during the trial, and (c) creates evaluability data that can be used to determine the evaluability of subjects at the end of the trial. Thus, this invention is a systematic methodology for timely, including immediate, data processing, summary, and feedback regarding subject performance in clinical trials.

These examples are meant to be illustrative and not limiting. The present invention has been described by way of example, and modifications and variations of the exemplary embodiments will suggest themselves to skilled artisans in this field without departing from the spirit of the invention. Features and characteristics of the above-described embodiments may be used in combination. The preferred embodiments are merely illustrative and should not be considered restrictive in any way. The scope of the invention is to be measured by the appended claims, rather than the preceding description, and all variations and equivalents that fall within the range of the claims are intended to be embraced therein.

Having described the invention, what is claimed as new and protected by Letters Patent is:

1. A method for classifying clinical trial results from one or more participants in a clinical trial, the method comprising:

a. entering evaluability data from the one or more participants on an electronic device, wherein the evaluability data comprise one or more evaluability data categories; and

b. comparing the evaluability data from the one or more evaluability data categories to a norm to classify the clinical trial results from the one or more participants in the clinical trial based on a type of compliance, wherein the classifying allows analysis of participants with a similar type of compliance.

2. The method of claim **1**, wherein the type of compliance comprises good compliance, non-compliance, or minor non-compliance.

3. The method of claim **1**, wherein the one or more evaluability data categories is used to determine the desirability of retaining the one or more participants in the trial or incorporating the one or more participants in the trial results.

4. The method of claim **1**, wherein the comparing comprises a quantitative analysis.

5. The method of claim **4**, wherein the quantitative analysis comprises a statistical or data mining technique.

6. The method of claim **5**, wherein the statistical or data mining technique comprises logistic regression, discriminant function analysis, classification and regression trees, neural networks, or multiple linear regression.

7. The method of claim **1**, wherein the one or more evaluability data categories comprise timeliness of data entry and another category.

8. The method of claim **7**, wherein the another category comprises consistency with other collected data, proximity of the data to an expected data range, and completeness of the data.

9. The method of claim **1**, wherein the comparing the evaluability data occurs during the clinical trial.

10. The method of claim **1**, further comprising generating at least one compliance enhancing feature.

11. The method of claim **10**, wherein the at least one compliance enhancing feature comprises a question to be posed to a user to determine a reason for non-compliance, an alarm tone, or a delay in reporting.

12. The method of claim **1**, wherein the norm is a historic norm.

13. The method of claim **1**, wherein the norm is a population norm.

14. The method of claim **1**, further comprising gathering the evaluability data in an evaluability database.

15. The method of claim **14**, wherein the evaluability database is a disease-specific database.

16. The method of claim **14**, wherein the evaluability database is a population-specific database.

17. The method of claim **14**, wherein the evaluability database is adapted to store data related to subject compliance.

18. The method of claim **1**, wherein the electronic device is a workstation.

19. The method of claim **1**, wherein the electronic device is a handheld electronic device.

20. The method of claim **19**, wherein the handheld electronic device is a handheld portable computer or phone.

21. The method of claim **1**, wherein the electronic device is connected to the Internet.

22. A computer readable medium having stored thereon sequences of instructions, which, when executed by a computer system, cause the computer system to perform:

a. entering evaluability data from one or more participants on an electronic device, wherein the evaluability data comprise one or more evaluability data categories; and

b. comparing the evaluability data from the one or more evaluability data categories to a norm to classify the clinical trial results from the one or more participants in the clinical trial based on a type of compliance, wherein the classifying allows analysis of participants with a similar type of compliance.

23. The computer readable medium of claim **22**, wherein the type of compliance comprises good compliance, non-compliance, or minor non-compliance.

24. The computer readable medium of claim **22**, wherein the one or more evaluability data categories is used to determine the desirability of retaining the one or more participants in the trial or incorporating the one or more participants in the trial results.

25. The computer readable medium of claim **22**, wherein the comparing comprises a quantitative analysis.

26. The computer readable medium of claim **25**, wherein the quantitative analysis comprises a statistical or data mining technique.

27. The computer readable medium of claim **26**, wherein the statistical or data mining technique comprises logistic regression, discriminant function analysis, classification and regression trees, neural networks, or multiple linear regression.

28. The computer readable medium of claim **22**, wherein the one or more evaluability data categories comprise timeliness of data entry and another category.

29. The computer readable medium of claim 28, wherein the another category comprises consistency with other collected data, proximity of the data to an expected data range, and completeness of the data.

30. The computer readable medium of claim 22, wherein the comparing the evaluability data occurs during the clinical trial.

31. The computer readable medium of claim 22, further comprising generating at least one compliance enhancing feature.

32. The computer readable medium of claim 31, wherein the at least one compliance enhancing feature comprises a question to be posed to a user to determine a reason for non-compliance, an alarm tone, or a delay in reporting.

33. The computer readable medium of claim 22, wherein the norm is a historic norm.

34. The computer readable medium of claim 22, wherein the norm is a population norm.

35. The computer readable medium of claim 22, further comprising gathering the evaluability data in an evaluability database.

36. The computer readable medium of claim 35, wherein the evaluability database is a disease-specific database.

37. The computer readable medium of claim 35, wherein the evaluability database is a population-specific database.

38. The computer readable medium of claim 35, wherein the evaluability database is adapted to store data related to subject compliance.

39. The computer readable medium of claim 22, wherein the electronic device is a workstation.

40. The computer readable medium of claim 22, wherein the electronic device is a handheld electronic device.

41. The computer readable medium of claim 40, wherein the handheld electronic device is a handheld portable computer or a phone.

42. The computer readable medium of claim 22, wherein the electronic device is connected to the Internet.

43. A system comprising an electronic device for entering evaluability data from one or more participants, wherein the evaluability data comprise one or more evaluability data categories, wherein the electronic device can compare the evaluability data from the one or more participants to a norm to classify the clinical trial results from the one or more participants in the clinical trial based on a type of compliance, wherein the classifying allows analysis of participants with a similar type of compliance.

44. The system of claim 43, wherein the type of compliance comprises good compliance, non-compliance, or minor non-compliance.

45. The system of claim 43, wherein the one or more evaluability data categories is used to determine the desirability of retaining the one or more participants in the trial or incorporating the one or more participants in the trial results.

46. The system of claim 43, wherein the comparing comprises a quantitative analysis.

47. The system of claim 46, wherein the quantitative analysis comprises a statistical or data mining technique.

48. The system of claim 47, wherein the statistical or data mining technique comprises logistic regression, discriminant function analysis, classification and regression trees, neural networks, or multiple linear regression.

49. The system of claim 43, wherein the one or more evaluability data categories comprise timeliness of data entry and another category.

50. The system of claim 49, wherein the another category comprises consistency with other collected data, proximity of the data to an expected data range, and completeness of the data.

51. The system of claim 43, wherein the comparing the evaluability data occurs during the clinical trial.

52. The system of claim 43, further comprising generating at least one compliance enhancing feature.

53. The system of claim 52, wherein the at least one compliance enhancing feature comprises a question to be posed to a user to determine a reason for non-compliance, an alarm tone, or a delay in reporting.

54. The system of claim 43, wherein the norm is a historic norm.

55. The system of claim 43, wherein the norm is a population norm.

56. The system of claim 43, further comprising gathering the evaluability data in an evaluability database.

57. The system of claim 56, wherein the evaluability database is a disease-specific database.

58. The system of claim 56, wherein the evaluability database is a population-specific database.

59. The system of claim 56, wherein the evaluability database is adapted to store data related to subject compliance.

60. The system of claim 43, wherein the electronic device is a workstation.

61. The system of claim 43, wherein the electronic device is a handheld electronic device.

62. The system of claim 61, wherein the handheld electronic device is a handheld portable computer or a phone.

63. The system of claim 43, wherein the electronic device is connected to the Internet.

* * * * *

US008433605B2

(12) **United States Patent**
Hufford et al.

(10) **Patent No.: US 8,433,605 B2**
(45) **Date of Patent: Apr. 30, 2013**

(54) **SYSTEM FOR CLINICAL TRIAL SUBJECT COMPLIANCE**

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USPC **705/11**; 705/3

(58) **Field of Classification Search** 705/2, 3, 705/4, 11
See application file for complete search history.

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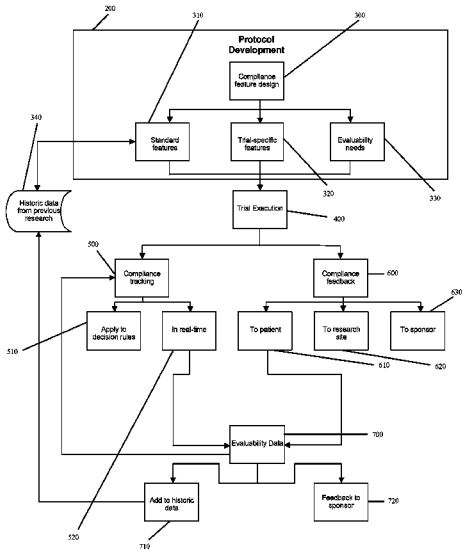
(57) **ABSTRACT**

The present invention is designed to develop research protocols for clinical trials. The invention also can track and enhance subject compliance with a research protocol. The invention further provides evaluability data related to subject performance in the clinical trial. According to an alternative embodiment of the invention, a portable electronic device is used to query and collect data from the subject.

63 Claims, 5 Drawing Sheets



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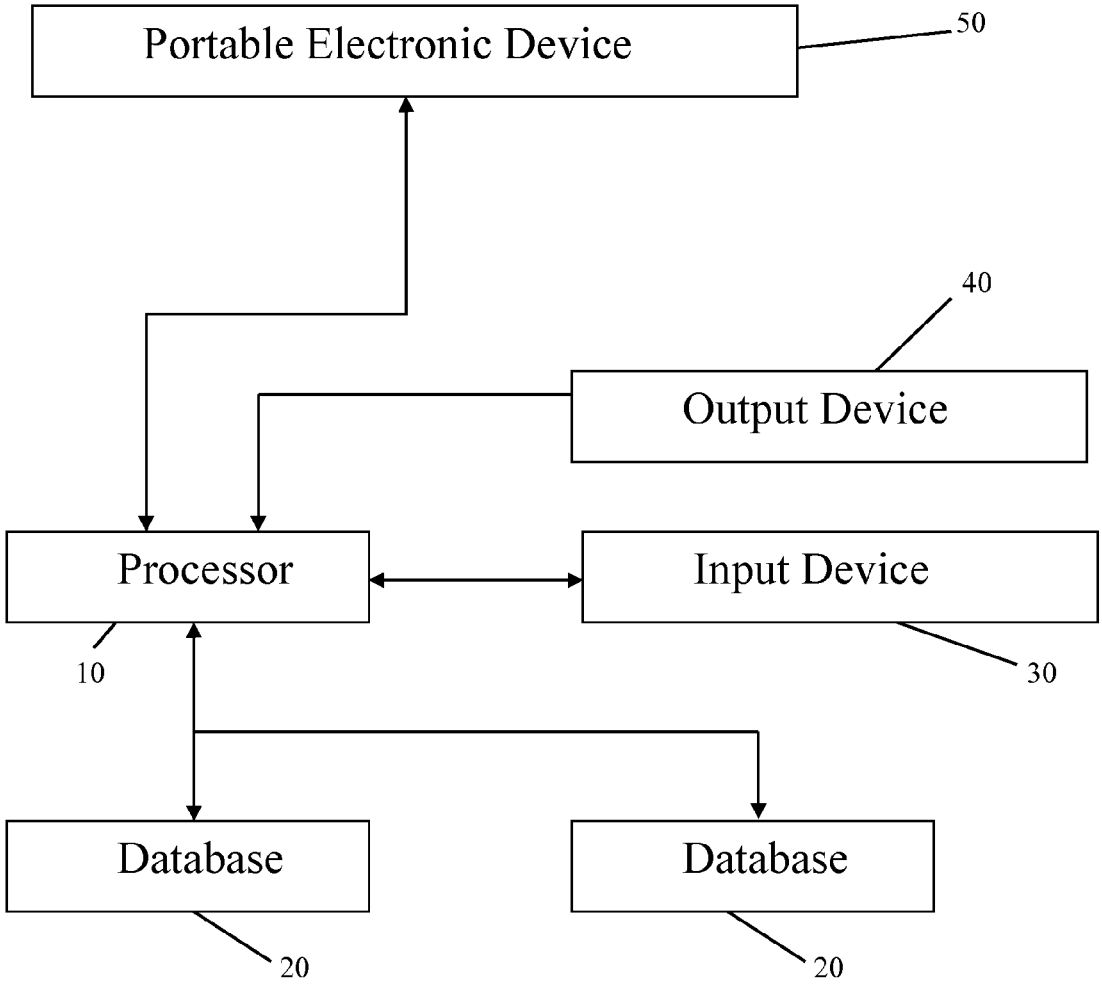
Portable Electronic Device
50
40
Output Device
Processor
Input Device
10
30
Database
Database
20
20

FIGURE 1

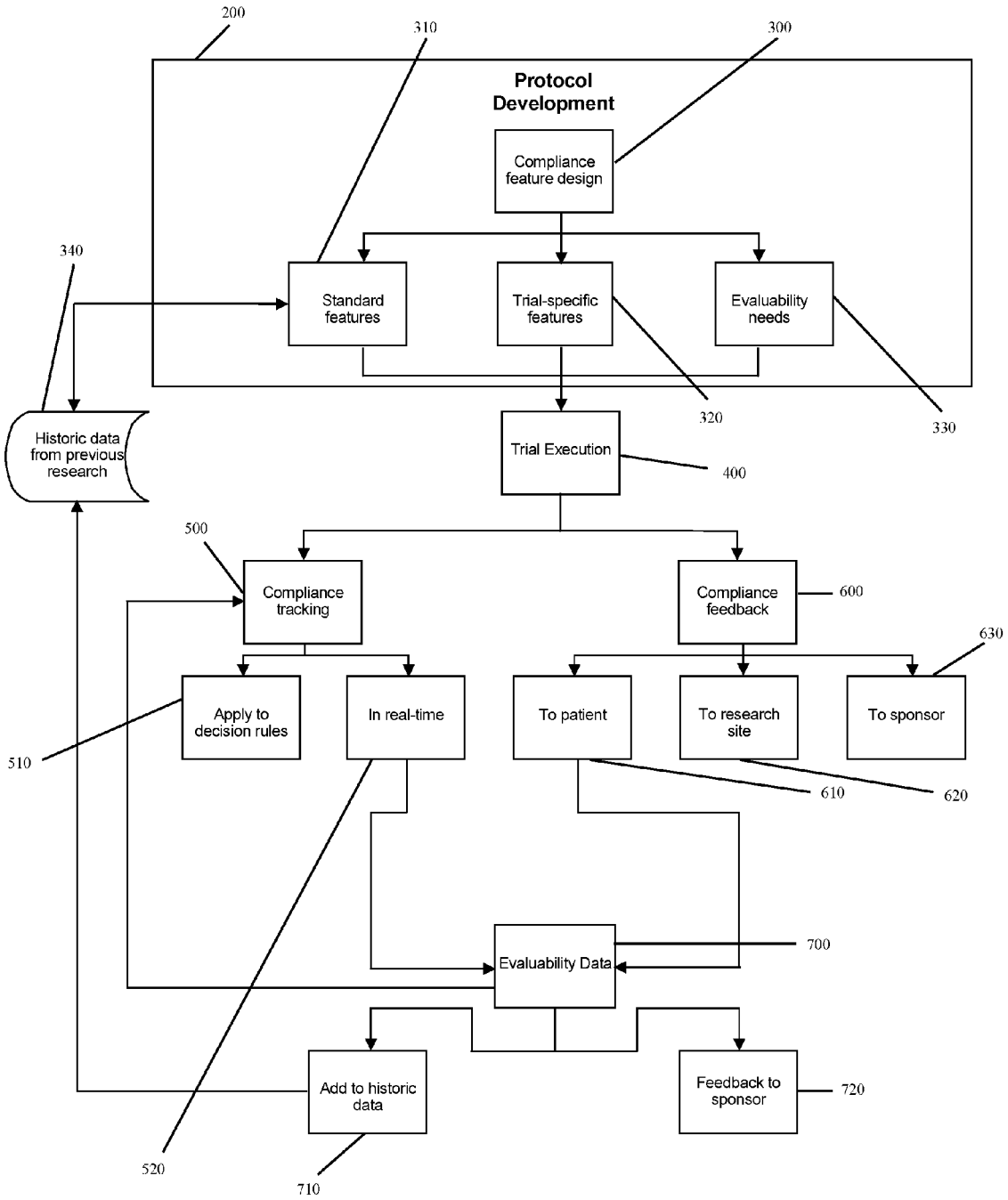
200
310
300
Protocol Development
Compliance feature design
340
Standard features
Trial-specific features
Evaluability needs
320
330
Historic data from previous research
Trial Execution
400
500
Compliance tracking
Compliance feedback
600
630
Apply to decision rules
In real-time
To patient
To research site
To sponsor
510
610
620
700
Evaluability Data
Add to historic data
Feedback to sponsor
720
520
710

FIGURE 2

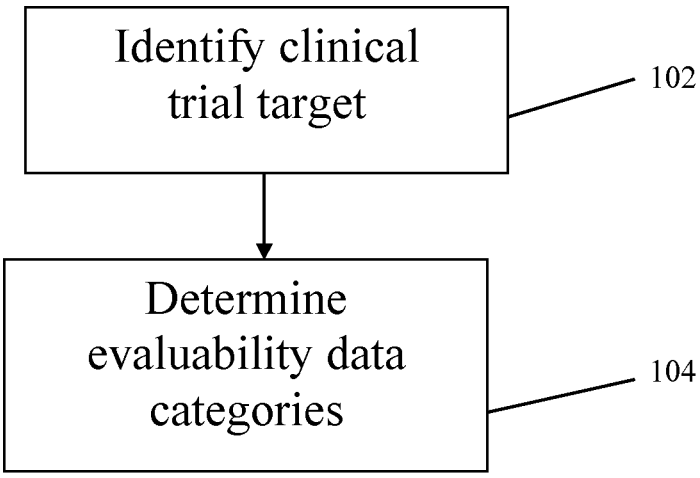
Identify clinical trial target
102
Determine evaluability data categories
104

FIGURE 3

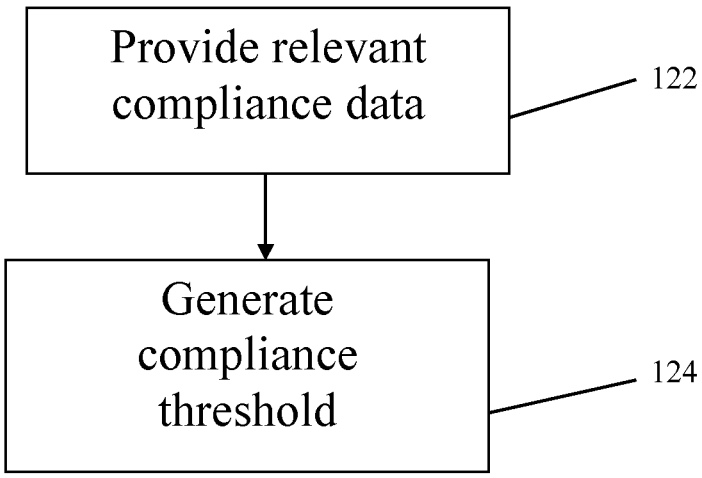
Provide relevant compliance data
122
Generate compliance threshold
124

FIGURE 4

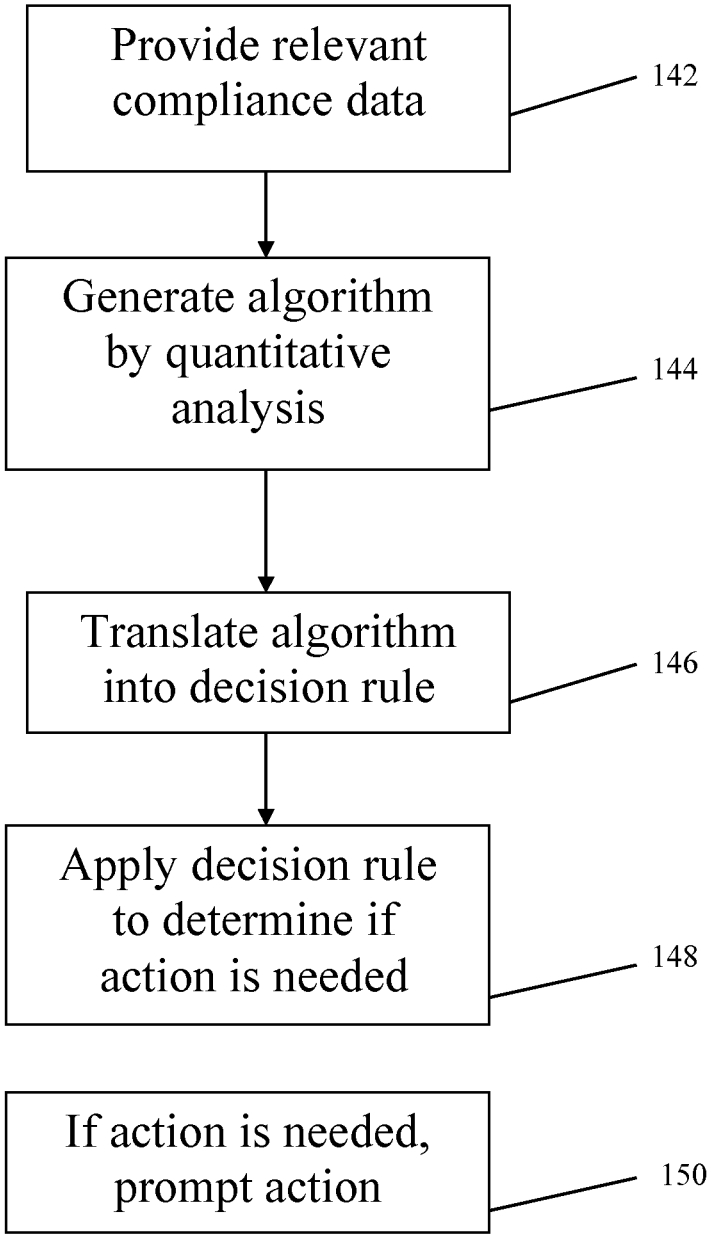
Provide relevant compliance data
142
Generate algorithm by quantitative analysis
144
Translate algorithm into decision rule
146
Apply decision rule to determine if action is needed
148
If action is needed, prompt action
150

FIGURE 5

SYSTEM FOR CLINICAL TRIAL SUBJECT COMPLIANCE

REFERENCE TO RELATED APPLICATIONS

This application is a continuation patent application of U.S. Utility application Ser. No. 13/211,133, filed Aug. 16, 2011, now U.S. Pat. No. 8,145,519, which is a continuation patent application of U.S. Utility application Ser. No. 09/825,533, filed Apr. 2, 2001, now U.S. Pat. No. 8,065,180; the subject matter of this application relates to the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", U.S. patent application Ser. No. 09/825,534, now U.S. Pat. No. 6,879,970, also filed on Apr. 2, 2001; the aforementioned applications, and the references cited therein, are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to conducting clinical trials. Specifically, the invention relates to research protocol development, management of subject behavior and distribution of evaluability data.

BACKGROUND OF THE INVENTION

Noncompliance with research protocols can be especially problematic, potentially resulting in unusable trial data. Typically, subjects are given a paper-based diary and asked to make scheduled entries regarding their illness, medication effects, as well as other data entries recording events as they happen. Subjects must keep track of the time of day, where they are in the sequence of events for any given day, and the appropriate procedures they are to follow across days. Many subjects do not complete their diaries or complete their diaries long after the events that are to be logged. Eight studies have examined compliance rates of these paper diaries by covertly collecting data about the timeliness of entries. A dramatic difference between subjects' reported versus actual compliance was observed. Whereas the paper diaries appeared to indicate high rates of compliance (88%), the actual rates of compliance were significantly lower (54%).

Evaluation of subject compliance with research protocols is often performed by examining only one variable at a time. Such evaluation is not empirically derived by quantitative analysis of existing datasets. Instead the evaluation relies on the researcher's judgment and biases to determine whether and what type of corrective action is required. Furthermore, evaluation of subject compliance with clinical trial protocols has typically not taken into account the domain of the clinical trial or the characteristics of the subjects.

SUMMARY OF THE INVENTION

The goal of clinical trials is to collect valid, reliable data on one or more conditions within a clinical trial group of subjects. Subjects in clinical trials are assigned tasks related to treatment and data collection in accordance with a research protocol. The integrity of clinical trials rests upon subjects' faithful performance of these tasks. If subjects fail to comply with the protocol, the trial will fail to yield reliable, valid trial data or results. Thus, subject noncompliance in clinical trials is a significant risk and cost to the pharmaceutical industry. Accordingly, the creation of appropriate research protocol, management and enhancement of subject behavior and effective distribution of clinical trial data is of substantial value to clinical research.

The benefits of a system that can track and enhance subject compliance in a clinical trial include: reliable, valid data; increased statistical power, reduced clinical trial costs through smaller sample sizes; reduced time to complete the clinical trial; and, ultimately, reduced time to get a drug or medical device to market.

According to one embodiment of the invention, a method of protocol development for a clinical trial is provided. The method includes the steps of identifying a clinical trial target reflecting a goal of the clinical trial, determining desired evaluability data categories to be gathered pertaining to a participant in the clinical trial, wherein an evaluability data of at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in one or more of the trial results.

According to another embodiment of the invention, a method of determining preferred targets for subject compliance is provided, having the steps of providing at least one of the group of historical subject compliance data and historical protocol data and generating at least one preferred compliance threshold by quantitative analysis of at least one of the group of the historical subject compliance data and the historical protocol data.

Another embodiment of the invention provides a method of monitoring subject compliance and having the steps of providing historical subject compliance data, generating at least one algorithm reflective of the historical subject compliance by quantitative analysis of the historical subject compliance data and the historical protocol data, translating the at least one algorithm into at least one decision rule for analyzing subject compliance information, obtaining the subject compliance information, comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a method of determining subject compliance and having the steps of providing historical subject compliance data and historical protocol data, generating a spectrum of compliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data, obtaining subject compliance information, comparing the spectrum of compliance to the subject compliance information to determine if corrective action is needed, and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a method of predicting subject noncompliance and having the steps of providing historical subject compliance data, generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance data, translating the at least one predictive algorithm into at least one prediction rule, obtaining subject compliance information, comparing the subject compliance information to the at least one prediction rule to determine if action is needed, and prompting action if the step of comparing indicates that action is needed.

A further embodiment of the invention provides a method of enhancing subject compliance and having the steps of providing historical subject compliance data, generating at least one algorithm by quantitative analysis of the historical subject compliance data, translating at least one algorithm

into at least one decision rule, obtaining subject compliance information and comparing the subject compliance information to the at least one decision rule to determine if affirmative action is warranted.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a user and an alarm electrically coupled to the portable electronic device and having varying alarm tones, wherein the varying alarm tones are emitted by the alarm if the user does not comply with a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a user and an alarm electrically coupled to the portable electronic device and having a tactile alarm.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device examines the input and reviews the input for inconsistencies.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device increases an amount of prompting of the input from the participant upon an automated determination that the participant does not comply with a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a participant in the clinical trial, wherein the portable electronic device decreases an amount of prompting of the input from the participant upon an automated determination that the participant has reported a predetermined number of events other than in response to the prompting by the portable electronic device.

A further embodiment of the invention provides a compliance monitoring device for use in clinical trials, having a portable electronic device capable of displaying information and receiving and storing input from a user, wherein the user is provided feedback based on the determination of whether the user has followed a predetermined protocol for providing the input to the portable electronic device.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of identifying a clinical trial target reflecting a goal of the clinical trial, determining desired evaluability data categories to be gathered pertaining to a participant in the clinical trial, wherein an evaluability data of at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in at least one result of the clinical trial.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing at least one of the group of historical subject compliance data and historical protocol data and generating at least one preferred compliance threshold by quantitative analysis of at least one of the group of the historical subject compliance data and the historical protocol data.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one algorithm reflective of the historical subject compliance data by quantitative analysis of the historical subject compliance data, translating the at least one algorithm into at least one decision rule for analyzing subject compliance information and obtaining the subject compliance information. The steps further include comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

Another embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data and historical protocol data, generating a spectrum of compliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data, obtaining subject compliance information, comparing the spectrum of compliance to the subject compliance information to determine if corrective action is needed and prompting corrective action if the step of comparing indicates that corrective action is needed.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance data, translating the at least one predictive algorithm into at least one prediction rule, obtaining subject compliance information, comparing the subject compliance information to the at least one prediction rule to determine if action is needed and prompting action if the step of comparing indicates that action is needed.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data, generating at least one algorithm by quantitative analysis of the historical subject compliance data, translating the at least one algorithm into at least one decision rule and obtaining subject compliance information and comparing the subject compliance information to the at least one decision rule to determine if affirmative action is warranted.

A further embodiment of the invention provides a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of displaying information to the participant and prompting input from the participant, accepting the input from the participant and decreasing an amount of prompting of the input from the participant upon an upon an automated determination that the participant has reported a predetermined number of events other than in response to the prompting by the portable electronic device.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following description and apparent from the accompanying drawings.

FIG. **1** illustrates a system according to an embodiment of the present invention;

FIG. **2** provides a functional layout of one embodiment of the present invention;

FIG. **3** illustrates a method according to an embodiment of the present invention;

FIG. **4** illustrates a method according to an embodiment of the present invention; and

FIG. **5** illustrates a method according to an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The illustrative embodiment of the present invention is designed to develop research protocols for clinical trials, track and enhance subject compliance with protocol requirements and provide evaluability data related to subject performance in the clinical trial.

The illustrative embodiment involves an empirically derived set of algorithms and decision rules to predict, track and enhance subject compliance with research protocols. The illustrative embodiment uses algorithms and decision rules to provide an empirical approach for analysis of different types of subject noncompliance with research protocols. This actuarial approach to predicting and managing subject noncompliance with clinical trial protocols is consistent with empirical research demonstrating the superiority of actuarial prediction of human behavior as compared to subjective clinical judgment. According to an alternative embodiment of the invention, a portable electronic device is used to query and collect data from the subject.

As used herein "clinical trial" refers to a broad range of data collecting activities, including studies directed to monitoring of one or more conditions within a clinical trial group of subjects. One such example includes drug trials involving humans. As used herein "subject" refers to any participant in a clinical trial, whether or not the subject has any relationship to a doctor or other medical professional.

Data "evaluability" refers to the usefulness of the data for the intended clinical trial purpose. Various factors may affect data evaluability, principally the circumstances under which the data was collected and how closely the circumstances with the research protocol for the specific clinical trial.

"Trial data" or "clinical trial data" refers to data gathered for the principal purpose of the clinical trial. For example, trial data would include pain levels experienced by subjects in a pain medication clinical trial or craving levels in an anti-smoking medication clinical trial.

"Evaluability data" or "compliance data" or "compliance information" is data that relates to the circumstances under which the trial data was collected or other data pertaining to characteristics of the trial data or other evaluability data. Some examples include timeliness, consistency with other collected data, proximity of the data to an expected data range and completeness of the data.

"Historical protocol data" includes data specifying the research protocol of earlier clinical trials. Examples of historical protocol data can include questions posed to subjects, frequency of prompting of a subject during various times of the day or week, time allowed for subjects to respond to questions, requirements of subject behavior, and conditions mandating removal of a subject from specific analyses or from participation in the clinical trial.

As used herein "portable electronic device" refers to any electronic device that can be adapted for use by a subject and/or clinical staff for viewing and/or inputting information. Preferably, the portable electronic device will also have a visual, audible or tactile alarm to gain the attention of the subject. For example, a pager having a vibration alarm may be used as a portable electronic device. Further examples include, pagers with audible alarms and/or text messaging capabilities, a laptop computer or a cell phone. Preferably, according to the invention, a portable electronic device will be a handheld computer provided with a display and a data input feature, such as a touch-sensitive screen, or buttons to enable a subject to respond to questions posed on the display or to input unsolicited information. Examples of such portable electronic devices include the Palm Pilot by Palm, Inc or Windows-based devices running Pocket PC from Microsoft Corporation. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem and/or a network, such as a LAN or the Internet.

According to an embodiment of the present invention, a system is provided as shown in FIG. **1**. A processor **10** is provided and is adapted to communicate with at least one database **20**. As discussed below, the database preferably stores data related to subject compliance and associated research protocols. An input device **30** is also provided to allow the subject or another person to provide input to the processor **10**. The input device **30** may be a keyboard, a modem or other such device adapted for communication with the processor. An output device **40** is also preferably provided to receive and display information from the processor **10**. Examples of output devices **40** include a printer and a monitor.

In one embodiment of the invention, a portable electronic device **50** is provided and selectively operatively coupled to the processor **10**. The portable electronic device **50** can also include a processor and may serve as an alarm, an input device, an output device, and/or a database.

In one embodiment, the present invention includes software that resides on a portable electronic device. Preferably, the portable electronic device is a handheld portable computer.

In another embodiment, the present invention includes software that resides on a server. Optionally, the server may communicate with a computer or portable electronic device.

FIG. **2** provides a functional layout of an embodiment of the present invention. Protocol development **200** involves a review of the goals of the clinical trial to determine research protocol including subject compliance targets prior to the start of the clinical trial. Preferably, compliance targets are developed in accordance with the invention disclosed in the co-pending patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", Ser. No. 09/825,534. Optionally, protocol development **200** can involve analysis of and updates to the protocol while the clinical trial is underway. Therefore, in accordance with an optional embodiment of the present invention, protocol development **200** can occur during trial execution **400**.

The present invention preferably involves identification of compliance targets relevant to specific features of the research protocol prior to the start of the clinical trial. These compliance targets can then be used to track subject compliance. Once these compliance targets have been identified, compliance-enhancing features can optionally be developed for a specific clinical trial and can preferably be incorporated into the functionality of the portable electronic device.

It is also within the scope of the present invention to use empirically derived algorithms to determine the best compliance targets for a specific clinical trial by the use of the

quantitative analysis methods of the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", Ser. No. 09/825,534. These algorithms could identify non-intuitive combinations of variables derived from historical data from previous clinical trials. Combinations of different compliance targets identified from other clinical trials could be used to predict a set of variables to be tracked in order to maximize an ability to detect subject noncompliance. Preferably, algorithms are translated to decision rules to ease detection of subject noncompliance.

Examples of various types of data that may be collected according to an embodiment of the invention include variables that may represent 'non-intuitive' predictors such as: gender of the subject, disease severity, the time of the year, and the day of the week.

Protocol development **200** preferably includes compliance feature design **300** to incorporate features into the research protocol to enhance subject performance in complying with the research protocol. Compliance features are preferably active during the execution of the clinical trial. Compliance features may be provided by a portable electronic device driving the protocol for subjects by guiding the subject through the protocol, not requiring the subject to remember the details of all the research protocol. For example, the portable electronic device can activate an alarm to prompt the subject to view the device. The portable electronic device can then prompt the subject to answer appropriate questions to gather information as specified by the research protocol. Optionally, the portable electronic device can modify and tailor questions based on information provided by the subject or based on input from the clinical staff. Preferably, each subject is provided with a portable electronic device and will keep the portable electronic device in their possession at all times during the clinical trial.

By the use of the portable electronic device, the present invention also allows subjects to administer self-reports of trial data including subjective reports, such as pain reduction, objective symptom reporting, such as bowel movement or asthmatic episode and cognitive measures, such as arithmetic tasks or reaction time. The electronic device may also optionally be configured to synchronize with any portable physiological measurement device to gather data from, or communicate with, the physiological device.

Moreover, portable electronic devices can optionally track all aspects of their use, resulting in a comprehensive record of subject compliance with the research protocol. A preferred embodiment of the invention allows clinical trial staff to systematically collect data regarding subject compliance by tracking a variety of different components of compliance, as well as check compliance against empirically derived algorithms and decision rules of compliance. These empirically derived algorithms and decision rules allow the disclosed invention to examine the data for nonintuitive and complex combinations of predictors to proactively determine whether the observed pattern of interaction with the portable electronic device suggests noncompliance. The patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", Ser. No. 09/825,534 provides additional detail regarding such algorithms and decision rules.

The portable electronic device also preferably conducts ongoing compliance checks and gives the subject feedback about their performance. For example logical psychometric or other inconsistencies can be determined by the portable electronic device. Actions of the portable electronic device are preferably processed according to decision rules. The portable electronic device can also vary its behavior based on the subject's behavior. For example, prompt frequency may be delayed or increased, or louder prompts may be provided. Also, vibration or visual alerts can be generated. Evaluability data related to the activity conducted with a portable electronic device is preferably transferred from the portable electronic device to a database for collecting information from multiple portable electronic devices. Such a database is preferably a database hosted at a central location. In one embodiment of the invention, the database is hosted on PC-based server software and is preferably adapted for communication with other computers. Additional compliance checks are preferably performed on the server and feedback is given to subjects by clinical trial staff; the feedback could be face-to-face or remote. Finally, the evaluability data is used to determine the evaluability of subject data, and screen out subjects or parts of subjects' data during the data analysis and reporting of the clinical trial data or results. Thus, the present invention is preferably utilized from beginning to end of a clinical trial.

Compliance feature design **300** includes standard features **310**, trial specific features **320**, and evaluability needs **330**. Incorporating standard features **310** within the research protocol preferably involves review of historic data from previous research **340**, including prior operations of the invention on earlier clinical trials and other sources of data involving subject compliance and, preferably, associated research protocols. Preferably, standard features **310** incorporated into the protocol will be derived in accordance with co-pending patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", Ser. No. 09/825,534, and will involve historic data from related clinical trials. For example, a clinical trial related to a cardiovascular condition will preferably develop standard compliance features **310** from historic data involving cardiovascular clinical trials.

Many types of compliance enhancing features are possible. For example, to enhance subject compliance with regular monitoring of symptom severity, varying alarm tones could be used to engender compliance. For example, if subjects are prompted using an audible 'beep' to complete a symptom report, the tone may increase in volume and/or pitch to increase the probability that subjects will complete the report. Other examples of compliance-enhancing features include allowing subjects to delay a report if they are busy. Subjects can also initiate a brief suspension of monitoring if their activity precludes completion of a report, for example, while driving. The portable electronic device could automatically re-initiate monitoring after a set amount of time has elapsed, or alternatively the subject could re-initiate monitoring. These examples do not represent an exhaustive list of compliance enhancing features of the present invention.

According to a preferred embodiment of the present invention, the following data is gathered by the use of a portable electronic device: the number of completed assessments or the ratio to expected assessments; the number or percent of prompts from the portable electronic device for data input that were not replied to by the subject; a variety of time based variables, such as for example, a sleep/wake cycle, obtained by having the portable electronic device record when subjects went to sleep and awoke each day of the clinical trial; the amount of time a subject puts the portable electronic device in a suspend mode that temporarily prevents the diary from prompting the subject for a reply; how often and for how long subjects respond to a prompt by requesting the portable electronic device delay a reply period; the frequency with which a subject abandons the portable electronic device, for

example, how often does the subject's pattern of inactivity with the portable electronic device suggest he/she has ceased complying with the research protocol.

Trial specific features **320** may also be included in compliance feature design **300** and may include specific aspects related to the current clinical trial. For example, compliance targets can also be identified based on specific characteristics of the disease state or clinical judgment of the clinical staff. For example, if subjects typically report a certain number of disease episodes per day, the present invention may target episodes per day as one variable to be tracked during the clinical trial and will automatically prompt subjects if a disease episode is not reported every 5 hours.

Evaluability needs **330** may also be incorporated in compliance feature design **300** and may involve tailoring compliance features in order to maximize evaluability data or address specific sponsor requirements. Preferably, evaluability needs **330** will be an integral part of the initial design of the research protocol. An example of an evaluability need **330** is a requirement that subject must report at least 5 disease episodes per day to be included in a particular analysis. In this example, how many disease episodes reports each day may be identified as an important variable to be tracked during trial execution.

During and/or after trial execution **400**, compliance tracking **500** is performed and involves analyzing subject behavior data and comparing it to the research protocol. Compliance tracking data, e.g. evaluability data, is gathered during the clinical trial and compared to historic norms **510** during or after the clinical by the use of decision rules. Additional detail is provided in the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", Ser. No. 09/825,534.

According to a further embodiment of the invention, algorithms can be used with decision rules to automatically generate feedback to both subjects and research staff. For example, an algorithm predicting a pattern of intermittent noncompliance with one facet of a clinical trial protocol could trigger a prompt to the subject on the portable electronic device to remain vigilant. Feedback could also be generated to the research staff to address an issue with the subject. Because the algorithms and decisions are preferably based on formal, empirical, and quantitative criteria, subjectivity can be removed from these decisions, which in turn minimizes the potential for bias.

An embodiment of the present invention preferably tracks compliance with the research protocol expected of subjects, such as timely completion of reports and compliance with the medication regimen. To successfully assess and remediate subject performance in clinical trials, the present embodiment preferably tracks compliance at several levels. If a portable electronic device is used for data entry, compliance may be tracked at the moment of data entry by determining whether or not the entry falls within acceptable parameters of the protocol. For example, is a response to a prompt required to be completed in the morning timely, or is the response delayed until the afternoon. Compliance tracking can also examine the content of the data entry itself to determine whether or not the subject is being compliant with the research protocol. For example: inconsistencies among two or more responses given; subject claiming they are in their living room and swimming. Compliance tracking can also take place over some span of time, such as, for example, weekly, to examine patterns or rates of noncompliance over time. Compliance tracking can also be performed against data pertaining to the subject's behavior during the clinical trial. For example, trends in subject response times or in the responses themselves can be determined.

The present invention can optionally reduce the burden on a non-compliant subject in order to increase compliance rates by providing fewer prompts for information. Also, the present invention can reduce the number of prompts for a subject that has provided voluntary, unprompted information. In summary, the present invention can be interactive. The present invention is preferably configured to initially enhance compliance while evaluating compliance as the clinical trial progresses. Preferably, the present invention dynamically adjusts in response to the subject's behavior, in accordance with the decision rules.

Compliance feedback **600** may involve forwarding messages, activating alerts or taking some other action in order to provide information to the subject **610**, the clinical trial staff, including the research site **620**, or to the sponsor **630**. Such messages may be include, for example positive feedback, corrective feedback or a recommendation to dismiss a subject from the clinical trial.

To increase the benefit of the compliance tracking feature of the present invention, compliance feedback is preferably provided to subjects, the research site, and the clinical trial sponsor in a timely fashion. Compliance tracking and compliance feedback may be conducted in an ongoing, timely manner on the portable electronic device itself. Compliance tracking and compliance feedback can also occur later, after data has been transmitted to a database, such as a database on a central server. In such a case, compliance feedback instructions can be sent back to the portable electronic device to provide feedback to subjects. Feedback for subjects can optionally be directed to clinical trial staff for delivery to the subjects.

According to an embodiment of the invention, a portable electronic device or a computer, such as a workstation or a server, can automatically check incoming data against a decision rule to determine if the pattern of responses require that a compliance alarm be triggered. Optionally, other demographic variables can also be checked by a decision rule. If one or more decision rules note that a problematic pattern of noncompliance or potential noncompliance is being observed, a number of actions may be taken. Examples of such actions include: posting a message on a website to be reviewed by the sponsor or research site, sending an e-mail or other type of notification, such as an automated call, to the subjects or research site coordinator, instructing the portable electronic device to display a certain message to the subject, instructing the portable electronic device to call the site during the subject's next interaction with the device, etc. These checks can either be triggered manually or automatically upon receipt of the data from the field.

According to an embodiment of the invention, the computer can perform the compliance analyses of incoming data instead of the compliance analyses being conducted by the portable electronic device. For example, the computer can analyze incoming data and compute the ratio of missed to completed assessments. This would be appropriate if the method of collection of the data did not otherwise allow the compliance data to be generated. For example, such a method of collection may involve written forms or an instrumented device not capable of computations.

According to another embodiment of the invention, the computer can execute more extensive compliance analyses than are capable on a portable electronic device. For example, more memory or processing power may be required to use the item response theory to examine the probability that a series

of responses are likely as compared to an existing database of population norms for a given measure.

According to a further embodiment of the invention, the computer can aggregate a series of assessment data over time within or between subjects. These aggregated compliance analyses on the computer allow for greater capacity than may be capable on a portable electronic device.

According to an embodiment of the invention, the computer can provide data to be displayed. Data may be displayed at the computer itself or be transmitted to another location, such as via hardwired or wireless access to the computer, including a LAN or the Internet. The data can be processed to provide a graphical display to interested parties. Examples of those who may be interested in viewing the graphical representation of the compliance data include a site coordinator (who may be interacting with the subject), a clinical research organization (who may be responsible for study execution across a number of research locations), other agencies interested in the collection of the data, or the sponsor of the research.

According to another embodiment of the invention, the computer can provide ongoing aggregation of data across subjects to speed the time required to combine, clean, and make available final data.

The various features of the computer, such as a workstation or server, of the above embodiments of the invention may be used individually or in combination.

Subject changes in behavior in response to compliance feedback may also be assessed. That is, an embodiment of the present invention may assess subjects' behavior in response to feedback regarding their compliance with the research protocol. For example, the software can detect whether or not subjects have begun to follow the research protocol more closely as a function of having received previous feedback about their noncompliance with the protocol.

Compliance feedback can take many forms. Compliance feedback can be given to a subject at varying intervals at any location, ranging from frequent, timely feedback, to more episodic feedback based on aggregate measures of compliance. Systematic compliance feedback may be given to subjects to encourage continued compliance, remediate poor compliance, or administer rewards to subjects for their performance.

Compliance feedback may be given to the clinical trial staff. To maximize the impact of the compliance system on trial success, clinical trial staff preferably receives training in the monitoring and correcting of subject compliance according to the present invention.

In one embodiment, the present invention creates customized graphical summaries of compliance tracking data and produces standardized reports for delivery of compliance feedback to subjects, the research site and/or clinical trail staff. Research sites are instructed on how to give standardized feedback to subjects in order to remediate poor subject compliance.

The aggregation of this compliance feedback can optionally be compiled into subject and clinical trial status reports during the clinical trial. These reports are for the research site and/or sponsors, to be used in evaluating the progress of the clinical trial. These reports contain a summary of subjects' compliance with research protocol, and therefore are an indicator of data evaluability.

Compliance tracking data is timely **520** forwarded as it is collected to an evaluability database **700**. Aggregation of compliance data enhances evaluation of subjects, prompting methodologies and research sites. Aggregated compliance data also allows for subjects to be examined for evaluability analyses. Also, evaluability data may be incorporated in compliance tracking **500** decisions during the course of a clinical trial. The evaluability database **700** also can provide additional historic data **710** to be included in a historic data database **340** upon which further research protocols are developed, as appropriate. The evaluability database **700** is also preferably made available to clinical staff and research sponsors. By making the evaluability database **700** accessible to clinical trial sponsors, sponsors are able to participate in decision making regarding the management of the clinical trial as the clinical trial is conducted. Furthermore, sponsors are able to monitor the progress of a clinical trial as it proceeds.

Evaluability data can be gathered in an evaluability database: a database that contains information relevant to the evaluability or acceptability of data from each subject. Evaluability data represents data that is of significant benefit for clinical trial sponsors. The evaluability database allows clinical trial sponsors to have timely evaluability data regarding the quality and consistency of the trial data. An example of trial data is efficacy data on the impact of the drug or medical device on the subject. In other words, the evaluability data allows clinical trial sponsors to have data about the quality of the trial data.

One specific use of the evaluability database is to determine whether or not a specific subject's data would be used in an analysis. For example, an analysis may be limited to those subjects who met minimal criteria for compliance. Another specific use of the evaluability database is to determine desirable trial data for a specific subject or among multiple subjects. This use of evaluability data involves whether or not specific data points within one or more subjects' trial data would be used in an analysis. For example, among all subjects, only trial data from days when compliance met acceptance criteria may be desired. In each instance, the evaluability data becomes an important and unique source of information regarding trial data quality in a clinical trial.

Evaluability data can be aggregated to create global, as well as disease and population-specific databases. The result of this aggregation of evaluability data provides an ability to predict subject noncompliance in clinical trials. This prediction ability increases as more evaluability data is available.

Evaluability data may also be reviewed by clinical trial staff. The periodicity of the data review could range from weekly to instantaneous, optionally using wireless technology or a web site located on the Internet. During the data review, the data can be checked using algorithms or decision rules to determine whether the pattern of subject behavior up to that point in the clinical trial triggers a decision rule, which may therefore recommend a course of action. Courses of action may include, for example, providing feedback to the subject, the research site, the sponsor and/or the clinical trial staff. The review may examine data over varying time intervals to determine whether some type of corrective action is necessary. By the use of the present invention, evaluability data can be reviewed for critical patterns of factors related to noncompliance or other events, such as effectiveness of compliance enhancement measures, ranging from within-day assessments to patterns extending over many months of monitoring.

The portable electronic device is also preferably adapted to communicate with another computer to allow the clinical staff to consolidate the data from all subjects in the clinical trial into one location for review or processing. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem

and/or a network, such as a LAN or the Internet. For example, by the use of the Internet or a dial-up modem connection, a subject may submit information from the portable electronic device to the clinical staff from the subject's home.

In another embodiment, a portable electronic device or a computer is adapted to communicate with clinical trial equipment used for measuring, monitoring, controlling or recording data or a process of the clinical trial. Examples of such processes include administration of medication or monitoring of heart rates. The portable electronic device or a computer preferably automatically records desired data for incorporation in the clinical trial data or compliance data. A further example of clinical trial equipment is an instrumented bottle cap, which is capable of recording and/or reporting when a bottle is opened or closed.

In another embodiment, clock synchronization can be used to synchronize data from clinical trial equipment used for measuring, monitoring, controlling or recording data or a process of the clinical trial with data collected by a computer or portable electronic device for later analysis.

In another embodiment of the invention, a paper form, such as a case report form, can be used by the subject to record data. The data can then be entered into a database by the use of a portable electronic device or other computer at an appropriate time. Examples of case report forms include hand-written forms and forms that allow for machine readable marks to be made, enabling automated scanning of the case report forms during entry of the data into a computer.

In an alternative embodiment of the present invention, the methods of the present invention may be incorporated in instructions recorded on a medium suitable for use in an electronic device, such as a computer, computer network server or a portable electronic device. The medium can include, for example, a hard disk, RAM medium, diskette, CD-ROM or other optical or magnetic storage medium. The instructions can optionally be stored on a server that can be remote from the subject and/or clinical staff member.

According to a further embodiment of the invention, a flow chart illustrating a method of protocol development of the present invention is set forth in FIG. **3**. First, a clinical trial target reflecting a goal of the clinical trial is identified, step **102**. Next, desired evaluability data categories to be collected during the clinical trial are determined, step **104**. Preferably, the desired evaluability data categories pertain to a participant in the clinical trial. Preferably, at least one of the evaluability data categories is used to determine the desirability of retaining the participant in the trial or incorporating the participant in the trial results.

According to another embodiment of the invention, a method for determining preferred targets for subject compliance is illustrated in FIG. **4**. First, historical subject compliance data and historical protocol data are provided, step **122**. Next, at least one preferred compliance threshold is generated, step **124**. The preferred compliance threshold is preferably generated by quantitative analysis of the historical subject compliance data and the historical protocol data.

According to a further embodiment of the invention, a flow chart illustrating a method of the present invention is set forth in FIG. **5**. First, relevant subject compliance data, and associated protocol data, reflecting subject compliance with research protocols in clinical trials is provided, step **142**. Subject compliance data and associated protocol data is preferably stored in one or more databases **20** and may be gathered from earlier clinical trials and/or earlier activities of a current clinical trial. Optionally, only subject compliance data may be stored, as some applications of the present invention may not require knowledge of associated historical protocol for use of the subject compliance data. For example, analysis of response times to questions may not require knowledge of the maximum permissible time for subjects to answer questions in earlier clinical trials. An output of the present invention preferably includes a database to provide subject compliance data and, preferably, associated protocol data, for later use by the invention.

Next, at least one algorithm representative of the subject compliance data is generated by quantitative analysis of the compliance data, step **144**. Preferably, multiple algorithms are generated. The present invention involves the application of statistical and other quantitative methods to screen existing research data for markers of, e.g. variables related to noncompliance with research protocols. Preferably, the subject compliance data is also reviewed to exclude invalid data. For example, data reported by one subject that appears to be well outside a range established by all other subjects can indicate invalid data.

Quantitative analysis methods are used to distinguish, identify, and predict instances of good and poor compliance. The quantitative analysis methods of the present invention may include, but are not limited to, application of a variety of statistical and data mining techniques, such as logistic regression, discriminant function analysis, classification and regression trees, neural networks, and multiple linear regression to screen existing data and derive algorithms to identify markers of noncompliance with research protocols.

Once the one or more algorithms of the invention have been derived from analysis of existing data, the algorithms can be translated into specific decision rules, step **146**. Decision rules are essentially reformatted algorithms that can be applied to current subject compliance data to determine whether action is needed, step **148**. Decision rules may determine a threshold of compliance or a threshold of noncompliance. Optionally, a decision rule may identify a spectrum of noncompliance, from minor noncompliance needing only corrective feedback, to significant noncompliance requiring subject removal from the clinical trial. Decision rules may be based on the specific dependent variable used to derive the algorithm or may be based on one or more differing variables.

Decision rules may be translated from algorithms that identify patterns of non-compliance data that are harbingers or leading indicators of later, more serious, non-compliance. This would allow early action to be taken based on these indicators. Such decision rules would typically be in the form of contingencies or conditions based on early compliance indicators.

Optionally, translation of algorithms to decision rules may involve human input or additional factors. For example, balancing the impact of a decision rule against the focus of the clinical trial may result in an alteration of the decision rule. For example, if subjects' heart rates are being monitored, frequency of prompting or loudness of reminder alerts may be minimized so as not to artificially raise subject heart rates. Also, clinical staff may alter decision rules based on their assessment of external factors outside of the scope of the quantitative analysis. An example may include providing more alerts to clinical staff instead of directly to subjects to provide more interaction between clinical staff and the subjects.

A decision rule may also be used to predict which subjects will fail to complete a clinical trial protocol. Therefore, a decision to rule to drop the subject from the clinical trial, or to work to improve subject performance, can be made at an early time. By providing those conducting a clinical trial with early feedback regarding subject noncompliance with a research protocol, the present invention improves clinical trial data

quality and may potentially save both time and money by either improving the compliance of potentially noncompliant subjects or excluding unimprovable noncompliant subjects early in a clinical trial.

If action is determined to be needed, action is prompted, step **150**. Examples of various actions include corrective action, compliance enhancing action, additional prompting of questions, reduced prompting of questions and sending an alert to the clinical staff to discuss an issue with the subject.

Additional detail regarding the method illustrated in FIG. **5** is provided in the patent application titled "Apparatus and Method for Prediction and Management of Subject Compliance in Clinical Research", Ser. No. 09/825,534.

The present invention can yield very high rates of compliance with real-time, real world data collection by subjects. In one embodiment, the present invention for clinical trials (a) builds compliance features and checks into the software that drives the protocol, (b) tracks and optionally gives feedback regarding compliance during the trial, and (c) creates evaluability data that can be used to determine the evaluability of subjects at the end of the trial. Thus, this invention is a systematic methodology for timely, including immediate, data processing, summary, and feedback regarding subject performance in clinical trials.

These examples are meant to be illustrative and not limiting. The present invention has been described by way of example, and modifications and variations of the exemplary embodiments will suggest themselves to skilled artisans in this field without departing from the spirit of the invention. Features and characteristics of the above-described embodiments may be used in combination. The preferred embodiments are merely illustrative and should not be considered restrictive in any way. The scope of the invention is to be measured by the appended claims, rather than the preceding description, and all variations and equivalents that fall within the range of the claims are intended to be embraced therein.

Having described the invention, what is claimed as new and protected by Letters Patent is:

1. A method for classifying results from one or more participants in a clinical trial, the method comprising:

a. electronically accessing evaluability data obtained during the clinical trial, wherein the evaluability data is from the one or more participants in the clinical trial, wherein the evaluability data is stored on an electronic device, wherein the evaluability data comprise data from one or more evaluability data categories;

b. comparing the evaluability data from the one or more evaluability data categories to a norm to classify clinical trial results from each of the one or more participants in the clinical trial based on a type of compliance; and

c. analyzing the classified clinical trial results from the one or more participants with a similar type of compliance.

2. The method of claim **1**, wherein the type of compliance comprises good compliance, non-compliance, or minor non-compliance.

3. The method of claim **1**, wherein the one or more evaluability data categories are used to determine a desirability of retaining the one or more participants in the clinical trial or incorporating the evaluability data from the one or more participants in the clinical trial results.

4. The method of claim **1**, wherein the comparing comprises a quantitative analysis.

5. The method of claim **4**, wherein the quantitative analysis comprises a statistical or data mining technique.

6. The method of claim **5**, wherein the statistical or data mining technique comprises logistic regression, discriminant function analysis, classification and regression trees, neural networks, or multiple linear regression.

7. The method of claim **1**, wherein the one or more evaluability data categories comprise timeliness of data entry and another category.

8. The method of claim **7**, wherein the another category comprises consistency with other collected data, proximity of the data to an expected data range, or completeness of the data.

9. The method of claim **1**, wherein the comparing the evaluability data occurs during the clinical trial.

10. The method of claim **1**, further comprising generating at least one compliance enhancing feature.

11. The method of claim **10**, wherein the at least one compliance enhancing feature comprises a question to be posed to a user to determine a reason for non-compliance, an alarm tone, or a delay in reporting.

12. The method of claim **1**, wherein the norm is a historic norm.

13. The method of claim **1**, wherein the norm is a population norm.

14. The method of claim **1**, further comprising gathering the evaluability data in an evaluability database.

15. The method of claim **14**, wherein the evaluability database is a disease-specific database.

16. The method of claim **14**, wherein the evaluability database is a population-specific database.

17. The method of claim **14**, wherein the evaluability database is adapted to store data related to subject compliance.

18. The method of claim **1**, wherein the electronic device is a workstation.

19. The method of claim **1**, wherein the electronic device is a handheld electronic device.

20. The method of claim **19**, wherein the handheld electronic device is a handheld portable computer or phone.

21. The method of claim **1**, wherein the electronic device is connected to the Internet.

22. A computer readable medium having stored thereon sequences of instructions, which, when executed by a computer system, cause the computer system to perform:

a. electronically accessing evaluability data obtained during a clinical trial, wherein the evaluability data is from one or more participants in the clinical trial, wherein the evaluability data is stored on an electronic device, wherein the evaluability data comprise data from one or more evaluability data categories;

b. comparing the evaluability data from the one or more evaluability data categories to a norm to classify clinical trial results from the one or more participants in the clinical trial based on a type of compliance; and

c. analyzing the classified clinical trial results from the one or more participants with a similar type of compliance.

23. The computer readable medium of claim **22**, wherein the type of compliance comprises good compliance, non-compliance, or minor non-compliance.

24. The computer readable medium of claim **22**, wherein the one or more evaluability data categories are used to determine a desirability of retaining the one or more participants in the trial or incorporating the evaluability data from the one or more participants in the trial results.

25. The computer readable medium of claim **22**, wherein the comparing comprises a quantitative analysis.

26. The computer readable medium of claim **25**, wherein the quantitative analysis comprises a statistical or data mining technique.

27. The computer readable medium of claim **26**, wherein the statistical or data mining technique comprises logistic

regression, discriminant function analysis, classification and regression trees, neural networks, or multiple linear regression.

28. The computer readable medium of claim **22**, wherein the one or more evaluability data categories comprise timeliness of data entry and another category.

29. The computer readable medium of claim **28**, wherein the another category comprises consistency with other collected data, proximity of the data to an expected data range, or completeness of the data.

30. The computer readable medium of claim **22**, wherein the comparing the evaluability data occurs during the clinical trial.

31. The computer readable medium of claim **22**, further comprising generating at least one compliance enhancing feature.

32. The computer readable medium of claim **31**, wherein the at least one compliance enhancing feature comprises a question to be posed to a user to determine a reason for non-compliance, an alarm tone, or a delay in reporting.

33. The computer readable medium of claim **22**, wherein the norm is a historic norm.

34. The computer readable medium of claim **22**, wherein the norm is a population norm.

35. The computer readable medium of claim **22**, further comprising gathering the evaluability data in an evaluability database.

36. The computer readable medium of claim **35**, wherein the evaluability database is a disease-specific database.

37. The computer readable medium of claim **35**, wherein the evaluability database is a population-specific database.

38. The computer readable medium of claim **35**, wherein the evaluability database is adapted to store data related to subject compliance.

39. The computer readable medium of claim **22**, wherein the electronic device is a workstation.

40. The computer readable medium of claim **22**, wherein the electronic device is a handheld electronic device.

41. The computer readable medium of claim **40**, wherein the handheld electronic device is a handheld portable computer or a phone.

42. The computer readable medium of claim **22**, wherein the electronic device is connected to the Internet.

43. A system comprising an electronic device for storing evaluability data obtained during a clinical trial, wherein the evaluability data is from one or more participants in the clinical trial, wherein the evaluability data comprise data from one or more evaluability data categories, wherein the electronic device can compare the evaluability data from the one or more participants in the clinical trial to a norm to classify clinical trial results from the one or more participants in the clinical trial based on a type of compliance, wherein the electronic device can analyze the classified clinical trial results from the one or more participants with a similar type of compliance.

44. The system of claim **43**, wherein the type of compliance comprises good compliance, non-compliance, or minor non-compliance.

45. The system of claim **43**, wherein the one or more evaluability data categories are used to determine a desirability of retaining the one or more participants in the trial or incorporating the evaluability data from the one or more participants in the trial results.

46. The system of claim **43**, wherein the comparing comprises a quantitative analysis.

47. The system of claim **46**, wherein the quantitative analysis comprises a statistical or data mining technique.

48. The system of claim **47**, wherein the statistical or data mining technique comprises logistic regression, discriminant function analysis, classification and regression trees, neural networks, or multiple linear regression.

49. The system of claim **43**, wherein the one or more evaluability data categories comprise timeliness of data entry and another category.

50. The system of claim **49**, wherein the another category comprises consistency with other collected data, proximity of the data to an expected data range, or completeness of the data.

51. The system of claim **43**, wherein the comparing the evaluability data occurs during the clinical trial.

52. The system of claim **43**, further comprising generating at least one compliance enhancing feature.

53. The system of claim **52**, wherein the at least one compliance enhancing feature comprises a question to be posed to a user to determine a reason for non-compliance, an alarm tone, or a delay in reporting.

54. The system of claim **43**, wherein the norm is a historic norm.

55. The system of claim **43**, wherein the norm is a population norm.

56. The system of claim **43**, further comprising gathering the evaluability data in an evaluability database.

57. The system of claim **56**, wherein the evaluability database is a disease-specific database.

58. The system of claim **56**, wherein the evaluability database is a population-specific database.

59. The system of claim **56**, wherein the evaluability database is adapted to store data related to subject compliance.

60. The system of claim **43**, wherein the electronic device is a workstation.

61. The system of claim **43**, wherein the electronic device is a handheld electronic device.

62. The system of claim **61**, wherein the handheld electronic device is a handheld portable computer or a phone.

63. The system of claim **43**, wherein the electronic device is connected to the Internet.

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Shiffman et al.

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(54) **APPARATUS AND METHOD FOR PREDICTION AND MANAGEMENT OF SUBJECT COMPLIANCE IN CLINICAL RESEARCH**

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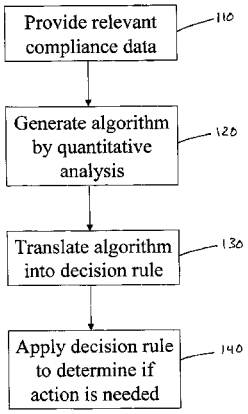
(57) **ABSTRACT**

A system for developing and implementing empirically derived algorithms to generate decision rules to predict subject noncompliance and fraud with research protocols in clinical trials allows for the identification of complex patterns of variables that detect or predict subject noncompliance and fraud with research protocol in the clinical trial. The present invention can also be used to monitor subject compliance with the research protocol to determine preferred actions to be performed. Optionally, the invention may provide a spectrum of noncompliance, from minor noncompliance needing only corrective feedback, to significant noncompliance requiring subject removal from the clinical trial. The algorithms and decision rules can also be domain-specific, such as detecting non-compliance or fraud among subjects in a cardiovascular drug trial, or demographically specific, such as taking into account gender or age which provides for algorithms and decision rules to be optimized for the specific sample of subjects being studied.

37 Claims, 2 Drawing Sheets



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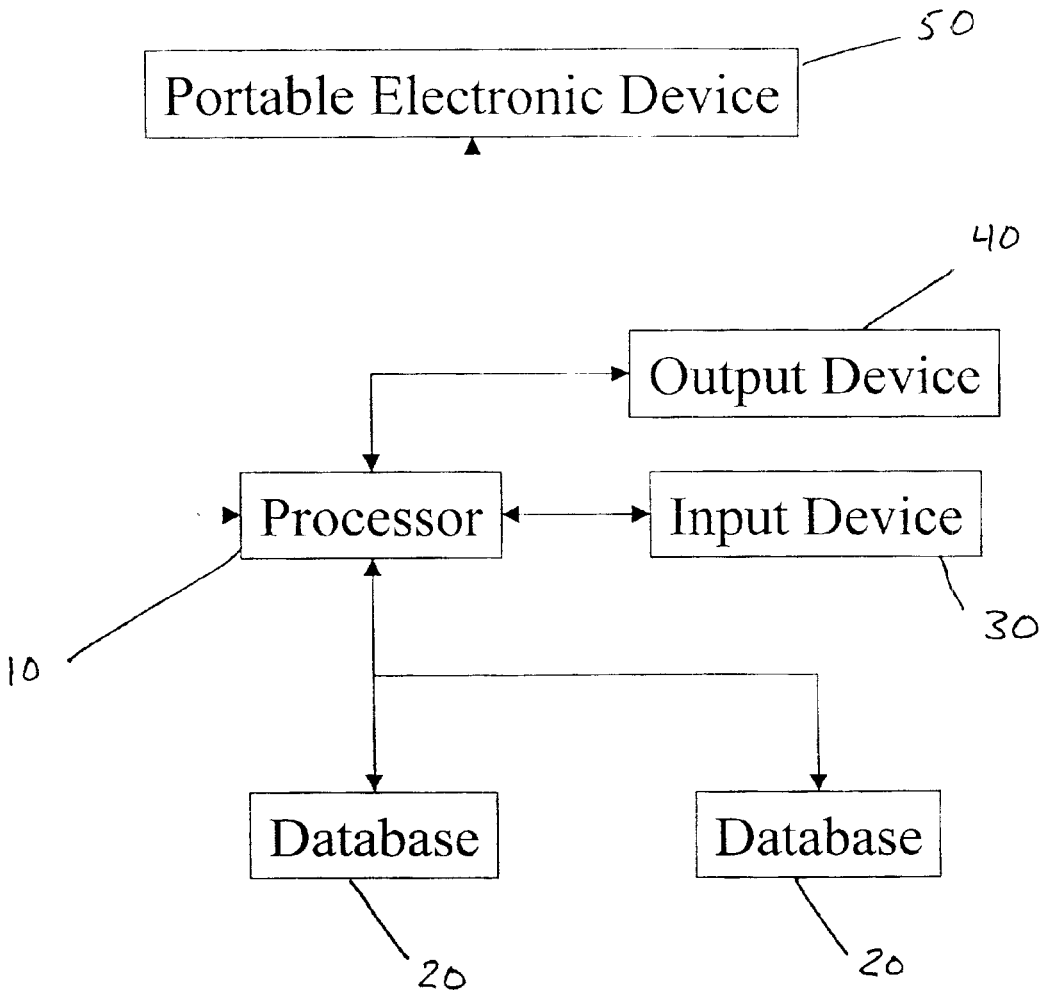
50
Portable Electronic Device
40
Output Device
Processor
Input Device
30
10
Database
Database
20
20

FIGURE 1

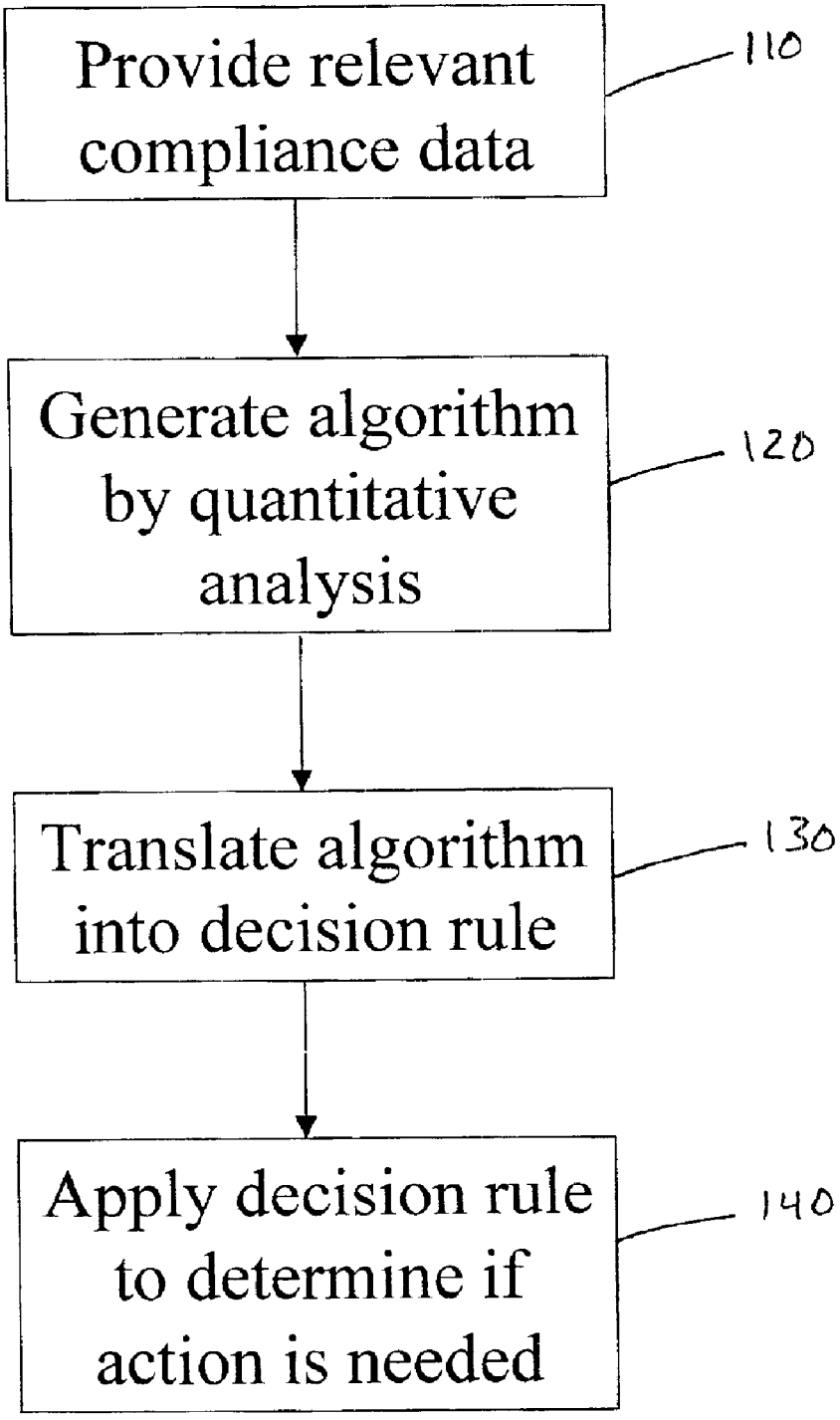
Provide relevant compliance data
110
Generate algorithm by quantitative analysis
120
Translate algorithm into decision rule
130
Apply decision rule to determine if action is needed
140

FIGURE 2

APPARATUS AND METHOD FOR PREDICTION AND MANAGEMENT OF SUBJECT COMPLIANCE IN CLINICAL RESEARCH

REFERENCE TO RELATED APPLICATIONS

The subject matter of this application relates to the patent application titled "System for Clinical Trial Subject Compliance", Ser. No. 09/825,533, and filed on even date herewith. The aforementioned application, and the references cited therein, are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to predicting subject behavior during research, especially clinical trials. Specifically, the invention relates to the prediction of subject noncompliance with protocols in clinical trials.

BACKGROUND OF THE INVENTION

Evaluation of subject compliance with research protocols typically looks at only one variable at a time. Such evaluation is not empirically derived by quantitative analysis of existing datasets, instead relying on the researcher's judgment and biases to determine whether and what type of corrective action is required. Furthermore, evaluation of subject compliance with clinical trial protocols has typically not taken into account the domain of the clinical trial or the characteristics of the subjects. Finally, such evaluation often cannot be made in a timely way, but is made only after serious noncompliance has already occurred.

SUMMARY OF THE INVENTION

The goal of clinical trials is to collect valid, reliable data on one or more conditions within a clinical trial group of subjects. Subjects in clinical trials are assigned tasks related to treatment and data collection in accordance with a research protocol. The integrity of clinical trials rests upon subjects' faithful performance of these tasks. If subjects fail to comply with the protocol, the trial fails to yield reliable, valid results. Thus, subject noncompliance in clinical trials is a significant risk and cost to the pharmaceutical industry. Accordingly, predicting subject performance and assessment of such performance is of substantial value to clinical research.

The benefits of a system that can predict and track subject compliance in a clinical trial include: reliable, valid data; increased statistical power; reduced clinical trial costs through smaller sample sizes; reduced time to complete the clinical trial; and, ultimately, reduced time to get a drug or medical device to market.

According to one embodiment of the invention, a method of predicting subject noncompliance is provided. The method includes the steps of providing historical subject compliance data, generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance data, and translating the at least one predictive algorithm into at least one prediction rule for use with a clinical trial.

According to another embodiment, a method of determining subject noncompliance includes the steps of providing at least one of the group of historical subject compliance data and historical protocol data and generating at least one algorithm reflective of at least one of historical subject compliance data and historical protocol data by quantitatively analyzing the historical subject compliance data and the historical protocol data. The method also includes translating the algorithm into at least one decision rule for analyzing subject compliance information, obtaining the subject compliance information and comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed.

According to a further embodiment, a method of the invention includes the steps of providing historical subject compliance data and historical protocol data, generating a spectrum of noncompliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data, obtaining subject compliance information and comparing the spectrum of noncompliance to the subject compliance information to determine if corrective action is needed.

According to an embodiment of the invention a method of detecting subject fraud is provided, having the steps of providing historical subject compliance data and historical protocol data, generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the historical subject compliance data and the historical protocol data and translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

According to an embodiment of the invention another method of detecting subject fraud is provided, having the steps of providing subject compliance data, generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the compliance data and translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

According to an embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions, having the steps of providing at least one of the group of historical subject compliance data and historical protocol data, generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of at least one of the group of the historical subject compliance data and the historical protocol data and translating the at least one predictive algorithm into at least one prediction rule for use with a clinical trial.

According to another embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing at least one of the group of historical subject compliance data and historical protocol data, generating at least one algorithm reflective of at least one of the group of the historical subject compliance data and the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data, translating the at least one algorithm into at least one decision rule for analyzing subject compliance information, obtaining the subject compliance information and comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed.

According to another embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data and historical protocol data, generating a spectrum of noncompliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical sub-

ject compliance data and the historical protocol data, obtaining subject compliance information and comparing the spectrum of noncompliance to the subject compliance information to determine if corrective action is needed.

According to a further embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical subject compliance data and historical protocol data, generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the historical subject compliance data and the historical protocol data and translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

According to an embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing subject compliance data, generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the compliance data and translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following description and apparent from the accompanying drawings.

FIG. **1** illustrates a system for determining subject noncompliance according to the teachings of the present invention; and

FIG. **2** is a schematic flow chart diagram illustrating the method according to the teachings of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention involves an empirically derived set of algorithms and decision rules to predict subject compliance, and detect noncompliance, with research protocols. The present invention uses algorithms and decision rules to provide an empirical approach for predicting different types of subject noncompliance with research protocols. This actuarial approach to predicting subject noncompliance with clinical trial protocols is consistent with empirical research demonstrating the superiority of actuarial prediction of human behavior as compared to subjective clinical judgment. According to an alternative embodiment of the invention, a portable electronic device is used to query and collect data from the subject.

As used herein "clinical trial" refers to a broad range of data collecting activities, including studies directed to monitoring of one or more conditions within a clinical trial group of subjects. One such example includes drug trials involving humans. As used herein "subject" refers to any participant in a clinical trial, whether or not the subject has any relationship to a doctor or other medical professional.

"Trial data" or "clinical trial data" refers to data gathered for the principle purpose of the clinical trial. For example, trial data would include pain levels experienced by subjects in a pain medication clinical trial or craving levels in an anti-smoking medication clinical trial.

"Evaluability data" or "compliance data" or "compliance information" is data that relates to the circumstances under which the trial data was collected or other data pertaining to characteristics of the trial data or other evaluability data. Some examples include timeliness, consistency with other collected data, proximity of the data to an expected data range and completeness of the data.

"Historical protocol data" includes data specifying the research protocol of earlier clinical trials. Examples of historical protocol data can include questions posed to subjects, frequency of prompting of a subject during various times of the day or week, time allowed for subjects to respond to questions, requirements of subject behavior, and conditions mandating removal of a subject from certain statistical analyses or removal as participant in the clinical trial.

As used herein "portable electronic device" refers to any electronic device that can be adapted for use by a subject and/or clinical staff for viewing and/or inputting information. Preferably, the portable electronic device will also have a visual, audible or tactile alarm to gain the attention of the subject. For example, a pager having a vibration alarm may be used as a portable electronic device. Further examples include, pagers with audible alarms and/or text messaging capabilities, a laptop computer or a cell phone. Preferably, according to the invention, a portable electronic device will be a handheld computer provided with a display and a data input feature, such as a touch-sensitive screen, or buttons to enable a subject to respond to questions posed on the display or to input unsolicited information. Examples of such portable electronic devices include the Palm Pilot by Palm, Inc or Windows-based devices running Pocket PC from Microsoft Corporation. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem and/or a network, such as a LAN or the Internet.

According to an embodiment of the present invention, a system is provided as shown in FIG. **1**. A processor **10** is provided and is adapted to communicate with at least one database **20**. As discussed below, the database preferably stores data related to subject compliance and associated research protocols. An input device **30** is also provided to allow the subject or another person to provide input to the processor **10**. The input device **30** may be a keyboard, a modem or other such device adapted for communication with the processor. An output device **40** is also preferably provided to receive and display information from the processor **10**. Examples of output devices **40** include a printer and a monitor.

In one embodiment of the invention, a portable electronic device **50** is provided and is selectively operatively coupled to the processor **10**. The portable electronic device **50** can also include a processor and may serve as an alarm, an input device, an output device, and/or a database. One example of a portable electronic device is a Palm Pilot by Palm, Inc, as described above.

According to an embodiment of the invention, a flow chart illustrating the method of the present invention is set forth in FIG. **2**. First, relevant subject compliance data, and associated protocol data, reflecting subject compliance with research protocols in clinical trials, is provided, step **110**. Optionally, only subject compliance data may be provided, as some application of the present invention may not require knowledge of associated historical protocol for use of the subject compliance data. For example, analysis of response times to questions may not require knowledge of the maximum permissible time for subjects to answer questions in earlier clinical trials.

Subject compliance data and associated protocol data is preferably stored in one or more databases **20** and may be

identified from earlier clinical trials and/or earlier activities of a current clinical trial. An output of the present invention preferably includes a database to provide subject compliance data and associated protocol data for later use by the invention.

The subject compliance data and associated protocol data is preferably specific to the type of condition or medication that is the focus of the clinical trial. For example, if the clinical trial relates to a cardiovascular condition, the data preferably relates to subject compliance with protocols in cardiovascular clinical trials. Likewise, if the clinical trial relates to a cardiovascular medication, the data used in the present invention will preferably relate to subject compliance with protocols in cardiovascular clinical trials. It is also within the scope of the invention to optionally include subject compliance data and associated protocol data obtained from an earlier phase of the clinical trial into the compliance data of the present invention. Alternatively, the subject compliance data and associated protocol data may not be related to the type of condition or medication that is the focus of the clinical trial.

Next, at least one algorithm representative of the subject compliance data is generated by quantitative analysis of the compliance data, step **120**. Preferably, multiple algorithms are generated. The present invention involves the application of statistical and other quantitative methods to screen existing research data for markers of, e.g. variables related to, noncompliance with research protocols. Preferably, the subject compliance data is also reviewed to exclude invalid data. For example, data reported by one subject that appears to be well outside a range established by all other subjects can indicate invalid data.

Examples of various types of data that may be collected according to an embodiment of the invention include variables that may represent 'non-intuitive' predictors such as: gender of the subject, disease severity, the time of the year, and the day of the week.

Quantitative analysis methods are used to distinguish, identify, and predict instances of good and poor compliance and/or instances of valid or invalid data entries. The quantitative analysis methods of the present invention may include, but are not limited to, application of a variety of statistical and data mining techniques, such as logistic regression, discriminant function analysis, classification and regression trees, neural networks, and multiple linear regression to screen existing data and derive algorithms to identify markers of noncompliance with research protocols.

Logistic regression analyses use dichotomous and continuous variables to predict dichotomous outcome variables. For example, dichotomous outcome variables can indicate "completed" or "failed to complete" a clinical trial monitoring protocol. Discriminant function analysis relates a categorical criterion variable to dichotomous or linear predictors. Classification and Regression Trees (CART) use binary recursive partitioning to identify unique groups of subjects, such as, for example, subjects failing to complete the clinical trial protocol and subjects completing the protocol with minimal corrective feedback regarding their compliance with the clinical trial protocol. Neural network approaches to pattern recognition examine data for patterns and classify certain patterns of data based on the probability that they lead to a given outcome. Multivariate Regressive Splines (MARS) build flexible regression models, including interactions, by fitting separate splines to distinct intervals of the predictor variables.

Other nonparametric and parametric statistical approaches can also be applied to the prediction of subject noncompliance with clinical trial protocols.

A variety of predictor and criterion variables can be used in the present invention. Predictor variables can range between basic demographic characteristics, such as, for example, gender, to specific clinical trial compliance related variables, such as, for example, mean latency to respond to an audible prompt from an optional portable electronic device. Similarly, criterion variables can range from subtle, such as, for example, missing some percentage of portable electronic device prompts, to severe noncompliance, such as, for example, failure to complete the clinical trial protocol. For detection of fraudulent entries, example predictor variables could include the speed or rate of entries, or an implausible or statistically unlikely pattern of answers to a set of assessment questions.

The present invention allows for complex, non-intuitive interactions among multiple variables to optimally predict subject compliance with clinical trial protocols. That is, the markers or variables used to predict noncompliance may or may not, in and of themselves, be related to noncompliance. Algorithms may rely on different variables for different subgroups. For example, subgroups can include, but are not limited to, men and women, older or younger subjects, or subjects late or early in the clinical trial. The algorithms may also identify different combinations of variables working only in tandem. Thus, the variables alone may not be directly, simply, or obviously related to noncompliance. The algorithms of the invention may use complex and nonintuitive combinations of predictors to predict subject noncompliance with clinical trial protocols.

The invention also allows context-specific algorithms to maximize predictive utility. That is, different algorithms can be derived for different groups of subjects, such as, for example, subjects with cardiovascular or central nervous system diseases. As a result, the present invention avoids assuming that any given set of variables will be equally predictive of clinical trial noncompliance for all types of conditions or diseases or for all types of subjects.

According to an embodiment of the invention, the present invention also provides for novel quantitative analyses to be incorporated into the development of algorithms to further improve their predictive validity. Specifically, the algorithms can be subject to continuous improvement as more data become available for analysis, either within an individual clinical trial or accumulating across clinical trials.

According to a further embodiment of the invention, algorithms can be used to determine appropriate feedback to both subjects and research staff regarding compliance with the protocol. For example, a computer program can implement decision rules based on these algorithms, and automatically determine appropriate feedback or action by the personnel involved in conducting the clinical trial.

An advantage of the present invention is that, because the algorithms and decisions are based on formal, empirical, and quantitative criteria, they remove the subjective element in these decisions, which in turn minimizes the potential for bias.

The above and other advantages provided by the disclosed invention include provisions for the application of these algorithms within existing and yet to be developed processes for giving systematic feedback to subjects, research sites, and clinical trial sponsors conducting clinical trials using clinical trials.

Once the one or more algorithms of the invention have been derived from analysis of existing data, the algorithms can be translated into specific decision rules, step **130**. Decision rules are essentially reformatted algorithms that

can be applied to current subject compliance data to determine whether action is needed, step **140**. Decision rules may determine a threshold of compliance or a threshold of noncompliance. Optionally, a decision rule may identify a spectrum of noncompliance, from minor noncompliance needing only corrective feedback, to significant noncompliance requiring subject removal from the clinical trial. Decision rules may be based on the specific dependent variable used to derive the algorithm or may be based on one or more differing variables.

For example, a subject who, within the first two days of the clinical trial, does not respond to more than 20% of prompted inquiries and either suspends prompting more than once or indicates he/she is napping more than once may be identified as failing to comply with the research protocol. As another example, subjects who suspend prompting at least twice, and whose total time of such suspension exceeds 2 hours, might be determined to be likely noncompliant, regardless of their overall performance. For purposes of illustration, one sample decision rule may be stated as:

Display noncompliance remediation message to clinical staff if:

[0.32(ratio of missed random prompts)+0.45(mean number of minutes spent time delaying assessments per day/100)+0.80(mean number of hours spent in sleep each night over past 7 days/10)]>1

where if noncompliance is determined by this decision rule, an action, such as sending a specific message to the clinical staff is recommended. For example, in the present example, the message "Subject is not following the protocol as required, resulting in substantial missed assessments. Call subject." may be determined to be the appropriate action.

According to an embodiment of the invention, criteria for identifying a subject as noncompliant with the research protocol need not overlap with criteria developed for determining whether to drop a subject from the clinical trial or exclude data related to that subject from the clinical trial results. For example, the decision rule(s) related to dropping a subject from the clinical trial might be based on failed responses to audible prompts rather than on suspension of prompting.

Typically, a decision rule specifies what type of action is required and may provide specific action details. Action types include corrective, affirmative and anti-fraud actions. Action details may include the content of a message to be provided to a subject or to clinical staff.

Decision rules may be translated from algorithms that identify patterns of noncompliance data that are harbingers or leading indicators of later, more serious, noncompliance. This would allow early action to be taken based on these indicators. Such decision rules would typically be in the form of contingencies or conditions based on early compliance indicators.

Optionally, translation of algorithms to decision rules may involve human input or additional factors. For example, balancing the impact of a decision rule against the focus of the clinical trial may result in an alteration of the decision rule. For example, if subjects' heart rates are being monitored, frequency of prompting or loudness of reminder alerts may be minimized so as not to artificially raise subject heart rates. Also, clinical staff may alter decision rules based on their assessment of external factors outside of the scope of the quantitative analysis. An example may include providing more alerts to clinical staff instead of directly to subjects to provide more interaction between clinical staff and the subjects.

A decision rule may also be used to predict which subjects will fail to complete a clinical trial protocol. Therefore, a decision to rule to drop the subject from the clinical trial, or to work to improve subject performance, can be made at an early time. By providing those conducting a clinical trial with early feedback regarding subject noncompliance with a research protocol, the present invention improves clinical trial data quality and may potentially save both time and money by either improving the compliance of potentially noncompliant subjects or excluding unimprovable noncompliant subjects early in a clinical trial.

The generation of a fraud detection algorithm can take many forms. The psychometric properties of the scale itself could be used to identify potentially fraudulent responses. For example, according to one embodiment of the invention, item response theory uses known properties of individual items within an assessment to estimate the probability that an observed pattern of responses is valid. Therefore, a subject answering yes to the question "My headaches are completely debilitating" has a low probability of also answering yes to the question "My headaches are a minor inconvenience" such that observing this pattern of responses could be indicative of fraud.

According to a further embodiment of the invention, the detection of fraudulent or invalid entries in subject-supplied data may be performed similarly to the methods described herein. For example, the analysis could be based on statistical properties of the responses themselves. Thus, as an example, analysis might indicate that when the standard deviation across subject responses on a particular questionnaire are less than 1.0, fraudulent or invalid completion is highly likely.

The content of subjects' responses could optionally be used as a source of data for the fraud detection algorithms if the responses are invariant or relatively invariant. For example, a subject answering 'yes' to all questions, even when the logical content of the questions would suggest some alternating pattern of appropriate responses.

Analysis of fraud could also be based on particular combinations of responses. Thus, subjects who answered that they took pain medication five or more times daily, but who elsewhere indicated either that pain severity was 4, on a scale of 1 to 10, or that pain frequency was 'infrequent' or 'rare', might be flagged as cases likely to be invalid. The response patterns determined to represent potentially fraudulent data need not be logically inconsistent or intuitively invalid. Rather, they are determined to represent potentially fraudulent data based on statistical analysis comparing valid and invalid response profiles. Therefore, questions posed to subjects can be tailored to provide opportunities for the subject to contradict, or appear in disagreement with, responses to earlier questions.

In an alternative embodiment, the posing of questions providing opportunities to contradict earlier responses can be interactive. For example, further questions providing opportunities to contradict earlier responses can be posed only if a response to a question appears unusual or if a decision rule indicates earlier indications of potential fraud.

As a further example, the time required for a subject to respond to items could be the foundation for the generation of fraud detection algorithms. For example, evaluability data could be used to estimate the mean length of time subjects take to respond to certain items. In such an example, response latencies less than two standard deviations below those norms could be the basis of identifying the responses as potentially fraudulent. For example, if a question contains 25 words and subjects take an average of 8 seconds to

answer the question, responses of less than 1 second could be identified as potentially fraudulent.

Alternatively, the portable electronic device could capture certain ecological data such as temperature or airborne particles, or physiological data, such as concurrent heart rate, suggestive of a particular location, subjective, or physical state, which is inconsistent with the subject's responses, suggesting possible fraud.

In an alternative embodiment of the invention, subjects can be included in the clinical trial for the purpose of providing fraudulent data. For example, in a group of 100 subjects, 20 subjects may be asked to provide fraudulent data. By having such fraudulent data among data provided by the subjects, the quantitative analysis of the present invention can be used to ensure the resulting algorithms and decision rules detect the known fraudulent entries. In the event other subjects are also fraudulently recording data without the knowledge of the clinical staff, the algorithms and decision rules will likely also detect such unknown fraudulent activity.

Each of the above variations for detection of fraud can be used according to various embodiment of the present invention individually, sequentially or in combination.

According to a preferred embodiment of the invention, the system of the invention for automated processing of data collected via a portable electronic device is provided. In this embodiment, the portable electronic device or system is designed to prompt a subject for information and/or collect information as recorded by the subject without prompting. Preferably, each subject in the clinical trial is provided with a portable electronic device. The portable electronic device is preferably used to collect compliance-relevant variables, such as the number of data entry episodes, missed data entry occasions (e.g., instances where the portable electronic device prompts for data, but the subject fails to respond). A database of these variables is preferably processed according to the decision rules to guide the actions of the portable electronic device as described in detail in the copending patent application titled "System for Clinical Trial Subject Compliance", Attorney Docket No. IVQ-002.

The portable electronic device is also preferably adapted to communicate with another computer to allow the clinical staff to consolidate the data from all subjects in the clinical trial into one location for review or processing. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem and/or a network, such as a LAN or the Internet. For example, by the use of the Internet or a dial-up modem connection, a subject may submit information from the portable electronic device to the clinical staff from the subject's home.

In another embodiment, a portable electronic device or a computer is adapted to communicate with clinical trial equipment used for measuring, monitoring, controlling or recording data or a process of the clinical trial. Examples of such processes include administration of medication or monitoring of heart rates. The portable electronic device or a computer preferably automatically records desired data for incorporation in the clinical trial data or compliance data.

In another embodiment of the invention, a paper form, such as a case report form, can be used by the subject to record data. The data can then be entered into a database by the use of a portable electronic device or other computer at an appropriate time. Examples of case report forms include hand-written forms and forms that allow for machine readable marks to be made, enabling automated scanning of the case report forms during entry of the data into a computer.

In an alternative embodiment of the present invention, the methods of the present invention may be incorporated in instructions recorded on a medium suitable for use in an electronic device, such as a computer, computer network server or a portable electronic device. The medium can include, for example, a hard disk, RAM medium, diskette, CD-ROM or other optical or magnetic storage medium. The instructions can optionally be stored on a server that can be remote from the subject or clinical staff member.

According to an embodiment of the invention, the server can provide data to be displayed. Data may be displayed at the server itself or be transmitted to another location, such as via hardwired or wireless access to the server, including a LAN or the Internet. The data can be processed to provide a graphical display to interested parties. Examples of those who may be interested in viewing the graphical representation of the compliance data include a site coordinator (who may be interacting with the subject), a clinical research organization (who may be responsible for study execution across a number of research locations), other agencies interested in the collection of the data, or the sponsor of the research.

According to another embodiment of the invention, the server can provide ongoing aggregation of data across subjects to speed the time required to combine, clean, and make available final data.

These examples are meant to be illustrative and not limiting. The present invention has been described by way of example, and modifications and variations of the exemplary embodiments will suggest themselves to skilled artisans in this field without departing from the spirit of the invention. Features and characteristics of the above-described embodiments may be used in combination. The preferred embodiments are merely illustrative and should not be considered restrictive in any way. The scope of the invention is to be measured by the appended claims, rather than the preceding description, and all variations and equivalents that fall within the range of the claims are intended to be embraced therein.

Having described the invention, what is claimed as new and protected by Letters Patent is:

1. A method of predicting subject noncompliance, comprising the steps of:

providing historical subject compliance data;

generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of the historical subject compliance; and

translating the at least one predictive algorithm into at least one prediction rule for use with a clinical trial.

2. The method of predicting subject noncompliance of claim **1**, further comprising the steps of:

obtaining subject compliance information; and

comparing the subject compliance information to the at least one prediction rule to determine if action is needed.

3. The method of predicting subject noncompliance of claim **2**, further comprising the step of determining an appropriate action if the step of comparing indicates that action is needed.

4. The method of predicting subject noncompliance of claim **2**, wherein the step of obtaining includes the step of employing a portable electronic device capable of displaying information and receiving and storing input from a user.

5. The method of predicting subject noncompliance of claim **2**, further comprising the step of creating an evaluability database adapted to store data related to subject compliance.

6. The method of predicting subject noncompliance of claim 5, wherein the evaluability database is tailored to a condition affecting the subject.

7. The method of predicting subject noncompliance of claim 1, wherein said step of providing includes providing historical protocol data and wherein said step of generating includes quantitative analysis of the historical protocol data.

8. The method of determining subject noncompliance of claim 1, wherein the step of providing employs at least one database containing at least one of the group of the historical subject compliance data and the historical protocol data.

9. A method of determining subject noncompliance, comprising the steps of:

providing at least one of the group of historical subject compliance data and historical protocol data;

generating at least one algorithm reflective of at least one of the group of the historical subject compliance data and the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data;

translating the at least one algorithm into at least one decision rule for analyzing subject compliance information;

obtaining the subject compliance information; and

comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed.

10. The method of determining subject noncompliance of claim 9, further comprising the step of determining an appropriate corrective action if the step of comparing indicates that corrective action is needed.

11. The method of determining subject noncompliance of claim 9, wherein the step of obtaining includes using a portable electronic device capable of displaying information and receiving and storing input from a user.

12. The method of determining subject noncompliance of claim 9, wherein the step of generating employs at least one of the group of multiple linear regression, discriminant function analysis, logistic regression, neural networks, classification trees and regression trees.

13. The method of determining subject noncompliance of claim 9, wherein the step of providing employs at least one database containing at least one of the group of the historical subject compliance data and the historical protocol data.

14. A method of determining subject noncompliance, comprising the steps of:

providing historical subject compliance data and historical protocol data;

generating a spectrum of noncompliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data;

obtaining subject compliance information; and

comparing the spectrum of noncompliance to the subject compliance information to determine if corrective action is needed.

15. The method of determining subject noncompliance of claim 14, further comprising the step of determining an appropriate corrective action if the step of comparing indicates that corrective action is needed.

16. The method of determining subject noncompliance of claim 15, wherein the step of obtaining includes using a portable electronic device capable of displaying information and receiving and storing input from a user.

17. A method of detecting subject fraud, comprising the steps of:

providing historical subject compliance data and historical protocol data;

generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the historical subject compliance data and the historical protocol data; and

translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

18. A method of detecting subject fraud, comprising the steps of:

providing subject compliance data;

generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the compliance data; and

translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

19. The method of detecting subject fraud of claim 18, further comprising the steps of:

comparing the subject compliance information to the at least one fraud detection rule to determine if action is needed.

20. The method of detecting subject fraud of claim 19, further comprising the step of determining an appropriate action if the step of comparing indicates that action is needed.

21. The method of detecting subject fraud of claim 19, wherein the step of providing includes the use of a portable electronic device capable of displaying information and receiving and storing input from a user.

22. The method of detecting subject fraud of claim 19, further comprising the step of creating an evaluability database adapted to store data related to subject fraud.

23. The method of detecting subject fraud of claim 22, wherein the evaluability database is tailored to a condition affecting the subject.

24. The method of detecting subject fraud of claim 18, wherein the step of providing employs at least one database containing at least one of the group of the historical subject compliance data and the historical protocol data.

25. A medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions comprising the steps of:

providing at least one of the group of historical subject compliance data and historical protocol data;

generating at least one predictive algorithm for predicting subject noncompliance by quantitative analysis of at least one of the group of the historical subject compliance data and the historical protocol data; and

translating the at least one predictive algorithm into at least one prediction rule for use with a clinical trial.

26. The medium of claim 25 having instructions further comprising the steps of:

obtaining subject compliance information; and

comparing the subject compliance information to the at least one prediction rule to determine if action is needed.

27. The medium of claim 25, wherein the step of obtaining includes the use of a portable electronic device capable of displaying information and receiving and storing input from a user.

28. The medium of claim 25 having instructions further comprising the step of creating an evaluability database adapted to store data related to subject compliance.

29. A medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions comprising the steps of:

providing at least one of the group of historical subject compliance data and historical protocol data;

generating at least one algorithm reflective of at least one of the group of the historical subject compliance data and the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data;

translating the at least one algorithm into at least one decision rule for analyzing subject compliance information;

obtaining the subject compliance information; and

comparing the subject compliance information to the at least one decision rule to determine if corrective action is needed.

30. The medium of claim **29** having instructions further comprising the step of determining an appropriate corrective action if the step of comparing indicates that corrective action is needed.

31. The medium of claim **29**, wherein the step of obtaining includes using a portable electronic device capable of displaying information and receiving and storing input from a user.

32. The medium of claim **29**, wherein the step of generating employs at least one of the group of multiple linear regression, discriminant function analysis, logistic regression, neural networks, classification trees and regression trees.

33. A medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions comprising the steps of:

providing historical subject compliance data and historical protocol data;

generating a spectrum of noncompliance representative of the historical subject compliance data not compliant with the historical protocol data by quantitative analysis of the historical subject compliance data and the historical protocol data;

obtaining subject compliance information; and

comparing the spectrum of noncompliance to the subject compliance information to determine if corrective action is needed.

34. The medium of claim **33** having instructions further comprising the step of determining an appropriate corrective action if the step of comparing indicates that corrective action is needed.

35. The medium of claim **34**, wherein the step of obtaining includes using a portable electronic device capable of displaying information and receiving and storing input from a user.

36. A medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions comprising the steps of:

providing historical subject compliance data and historical protocol data;

generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the historical subject compliance data and the historical protocol data; and

translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

37. A medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions comprising the steps of:

providing subject compliance data;

generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the compliance data; and

translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

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Shiffman et al.

(10) **Patent No.: US 7,415,447 B2**
(45) **Date of Patent: *Aug. 19, 2008**

(54) **APPARATUS AND METHOD FOR PREDICTION AND MANAGEMENT OF PARTICIPANT COMPLIANCE IN CLINICAL RESEARCH**

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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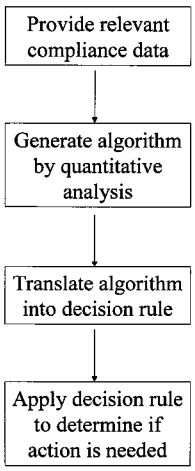
(57) **ABSTRACT**

A system for developing and implementing empirically derived algorithms to generate decision rules to determine participant noncompliance and fraud with research protocols in clinical trials allows for the identification of complex patterns of variables that detect or predict participant noncompliance and fraud with research protocol, including performance and enrollment goals, in the clinical trial. The data may be used to overall predict the performance of any participant in a clinical trial, allowing selection of participants that tend to produce useful, high-quality results. The present invention can also be used to monitor participant compliance with the research protocol and goals to determine preferred actions to be performed. Optionally, the invention may provide a spectrum of noncompliance, from minor noncompliance needing only corrective feedback, to significant noncompliance requiring participant removal from the clinical trial or from future clinical trials. The algorithms and decision rules can also be domain-specific, such as detecting non-compliance or fraud among subjects in a cardiovascular drug trial, or demographically specific, such as taking into account gender, age or location, which provides for algorithms and decision rules to be optimized for the specific sample of participants being studied.

30 Claims, 2 Drawing Sheets



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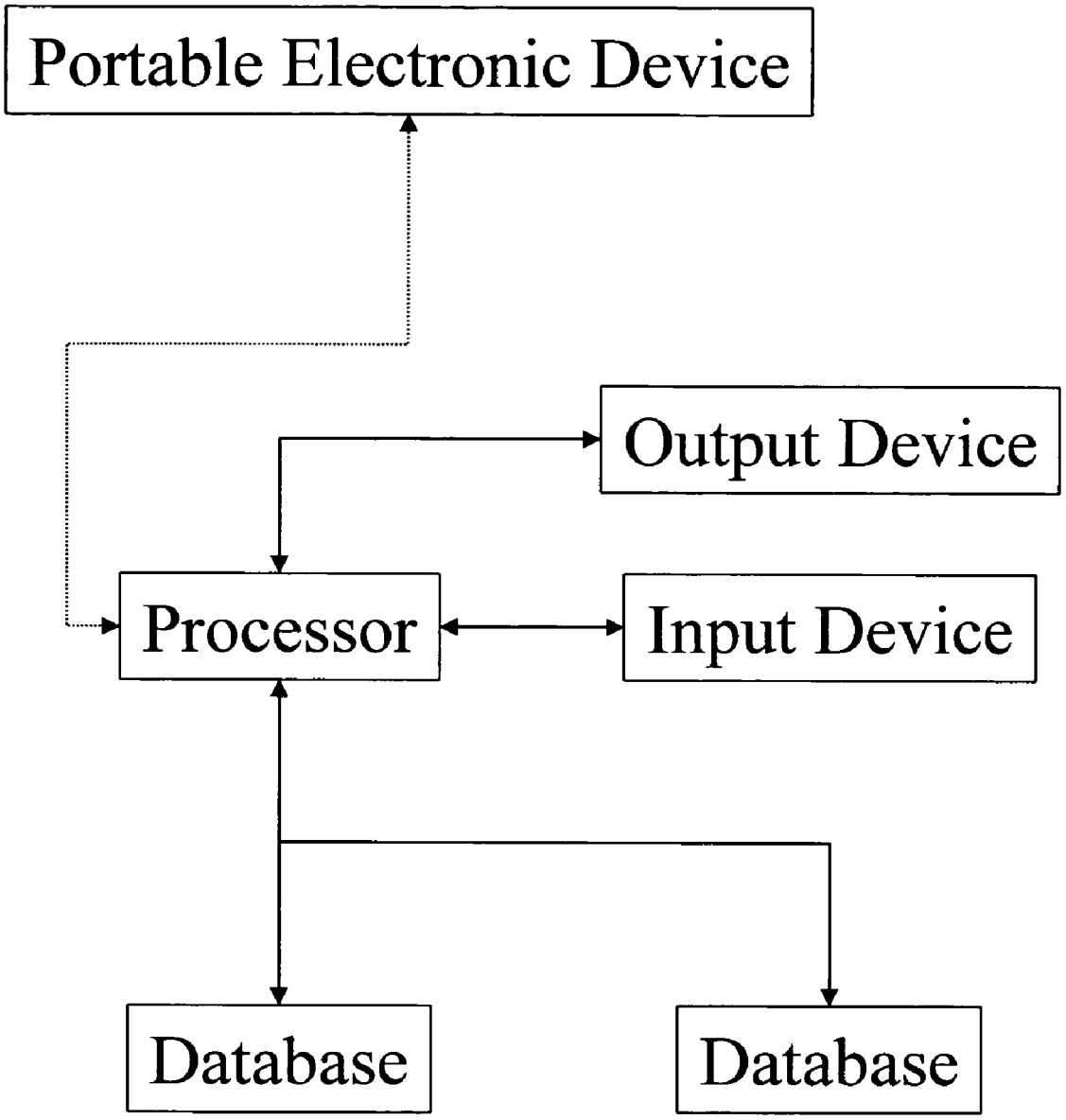
Portable Electronic Device
Output Device
Processor
Input Device
Database
Database

FIGURE 1

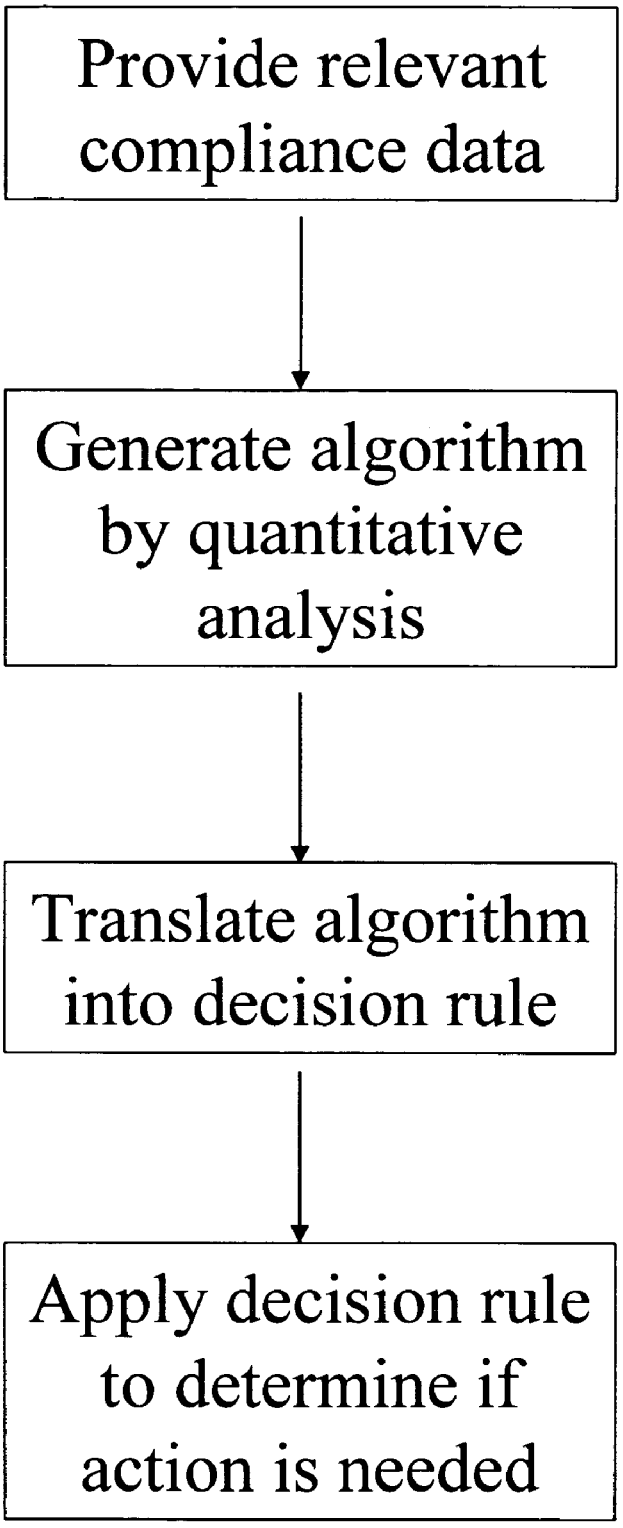
Provide relevant compliance data
Generate algorithm by quantitative analysis
Translate algorithm into decision rule
Apply decision rule to determine if action is needed

FIGURE 2

APPARATUS AND METHOD FOR PREDICTION AND MANAGEMENT OF PARTICIPANT COMPLIANCE IN CLINICAL RESEARCH

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent Ser. No. 11/002,046, which is a continuation of application Ser. No. 09/825,534 filed Apr. 2, 2001, now U.S. Pat. No. 6,879,970 issued Apr. 12, 2005. The subject matter of this application relates to the patent application titled "System for Clinical Trial Subject Compliance", application Ser. No. 09/825,533, filed Apr. 2, 2001. The aforementioned application, and the references cited therein, are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to predicting the behavior of a clinical trial participant during research, especially clinical trials. Specifically, the invention relates to the prediction of clinical trial participant compliance with protocols, including performance and enrollment goals, in clinical trials.

BACKGROUND OF THE INVENTION

Evaluation of the compliance of a clinical trial participant with research protocols, including research goals, typically looks at only one variable at a time. Such evaluation is not empirically derived by quantitative analysis of existing datasets, instead relying on the researcher's or sponsors' judgment and biases to determine whether and what type of corrective action is required. Furthermore, evaluation of compliance of a clinical trial participant with clinical trial protocols has typically not taken into account the domain of the clinical trial or the characteristics of the participants. Finally, such evaluation often cannot be made in a timely way, but is made only after serious noncompliance has already occurred.

Each year, many resources, including money and time, are wasted on clinical trial sites that fail to comply with research protocols, including failure to produce any data, a sufficient amount of data or reliable data. For example, many clinical trial sites provide inaccurate data due to poor training or non-compliance with research protocol. Resources may be devoted to clinical trial sites that fail to enroll a sufficient number of subjects, or even one subject, producing little useful data in view of the amount of resources devoted to setting up the clinical trial. Further, participants in the clinical, such as subjects, trial investigators, research coordinators, site staff, and study monitors, may on occasion falsify data for the trial, possibly resulting in erroneous conclusions and creating liability for the trial's sponsor. Therefore, identification of clinical trial sites or other clinical trial participants that tend to produce results that are adequate in quantity and quality, and those that do not produce adequate results may provide enormous conservation of resources.

SUMMARY OF THE INVENTION

The present invention provides a system and method for determining participant compliance in a clinical trial based on quantitative analysis of historical compliance data obtained by or about the participant. Compliance may relate to adherence to set procedures, achievement of certain goals of a clinical trial, or any other parameter indicative of performance. The historical compliance data may be obtained at any point previous to the quantitative analysis, such as at an earlier clinical trial, or at an earlier point in a clinical trial for which compliance is determined. The determination of compliance may predict future compliance or noncompliance, or identify past instances of compliance or noncompliance.

The goal of clinical trials is to collect valid, reliable data on one or more conditions within a clinical trial group of subjects. Subjects in clinical trials are assigned tasks related to treatment and data collection in accordance with a research protocol. The integrity of clinical trials rests upon subjects' faithful performance of these tasks, as well as the compliance of other clinical trial participants, such as doctors, nurses, the overall site and so on, with clinical trial protocol and its requirements. Compliance with clinical trial protocol is generally indicative of overall performance. If clinical trial participants fail to comply with the protocol, the trial fails to yield reliable, valid results. Thus, participant noncompliance in clinical trials is a significant risk and cost to the pharmaceutical industry. Accordingly, predicting participant performance, quality of data collected during a clinical trial, and assessment of such performance is of substantial value to clinical research.

The benefits of a system that can predict and track compliance of a participant in a clinical trial include: reliable, valid data; increased statistical power; reduced clinical trial costs through smaller sample sizes; reduced time to complete the clinical trial; conservation of resources by avoiding non-producing clinical trial participants, reduced noise in the data that would be introduced by poorly-performing investigators, research coordinators, and sites and, ultimately, reduced time to get a drug or medical device to market. The system may, for example, identify clinical trial sites that tend to do a poor job, such as those that provide less reliable or accurate data, provide poor training to subjects, produce few, if any, evaluative subjects, or produce little or no data, allowing sponsors or researchers to avoid using such sites for conducting a clinical trial.

According to one embodiment of the invention, a method of predicting noncompliance in a clinical trial participant is provided. The method includes the steps of providing historical compliance data for a clinical trial participant, and generating at least one predictive algorithm for predicting noncompliance of the clinical trial participant by quantitative analysis of the historical compliance data.

The at least one predictive algorithm may be translated into at least one prediction rule for use within either the on-going clinical trial, or for future application in other clinical trials.

In another embodiment of the invention, a method of identifying a suitable clinical trial site for conducting a clinical trial is provided, comprising the steps of providing a database storing historical compliance data for a plurality of clinical trial sites, performing a statistical analysis of the historical compliance data for each clinical trial site to predict compliance in a future clinical trial and selecting a clinical trial site that is predicted to comply with research protocols.

In another embodiment of the invention, a method of predicting success of a clinical trial involving a selected clinical trial participant is a provided. The method of predicting success comprises the steps of providing historical compliance data from a clinical trial involving the clinical trial participant and performing a quantitative analysis of the data to identify whether the participant is likely to produce data in compliance with research protocol in the future.

According to another embodiment, a method of determining noncompliance of a clinical trial participant includes the steps of providing at least one of the group of historical participant compliance data and historical protocol data and

generating at least one algorithm reflective of at least one of historical participant compliance data and historical protocol data by quantitatively analyzing the historical participant compliance data and the historical protocol data. The method also includes translating the algorithm into at least one decision rule for analyzing participant compliance information, obtaining the participant compliance information and comparing the participant compliance information to the at least one decision rule to determine if corrective action is needed.

According to a further embodiment, a method of the invention includes the steps of providing historical participant compliance data and historical protocol data, generating a spectrum of noncompliance representative of the historical participant compliance data not compliant with the historical protocol data by quantitative analysis of the historical participant compliance data and the historical protocol data, obtaining participant compliance information and comparing the spectrum of noncompliance to the participant compliance information to determine if corrective action is needed.

According to an embodiment of the invention a method of detecting fraud by a participant in a clinical trial is provided, having the steps of providing historical participant compliance data and historical protocol data, generating at least one fraud detection algorithm for detecting participant fraud by quantitative analysis of the historical participant compliance data and the historical protocol data and translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

According to an embodiment of the invention another method of detecting fraud by a participant in a clinical trial is provided, having the steps of providing participant compliance data, generating at least one fraud detection algorithm for detecting subject fraud by quantitative analysis of the compliance data and translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

According to an embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions, having the steps of providing at least one of the group of historical participant compliance data and historical protocol data, generating at least one predictive algorithm for predicting participant noncompliance by quantitative analysis of at least one of the group of the historical participant compliance data and the historical protocol data and translating the at least one predictive algorithm into at least one prediction rule for use with a clinical trial.

According to another embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing at least one of the group of historical participant compliance data and historical protocol data, generating at least one algorithm reflective of at least one of the group of the historical participant compliance data and the historical protocol data by quantitative analysis of the historical participant compliance data and the historical protocol data, translating the at least one algorithm into at least one decision rule for analyzing participant compliance information, obtaining the participant compliance information and comparing the participant compliance information to the at least one decision rule to determine if corrective action is needed.

According to another embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical participant compliance data and historical protocol data, generating

a spectrum of noncompliance representative of the historical participant compliance data not compliant with the historical protocol data by quantitative analysis of the historical participant compliance data and the historical protocol data, obtaining participant compliance information and comparing the spectrum of noncompliance to the participant compliance information to determine if corrective action is needed.

According to a further embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing historical participant compliance data and historical protocol data, generating at least one fraud detection algorithm for detecting participant fraud by quantitative analysis of the historical participant compliance data and the historical protocol data and translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

According to an embodiment of the invention a medium suitable for use in an electronic device and having instructions for execution on the electronic device, the instructions having the steps of providing participant compliance data, generating at least one fraud detection algorithm for detecting participant fraud by quantitative analysis of the compliance data and translating the at least one fraud detection algorithm into at least one fraud detection rule for use with a clinical trial.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following description and apparent from the accompanying drawings.

FIG. **1** illustrates a system for determining noncompliance of a participant in a clinical trial according to the teachings of the present invention; and

FIG. **2** is a schematic flow chart diagram illustrating the method according to the teachings of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention involves an empirically derived set of algorithms and decision rules to identify and/or predict compliance of a participant in a clinical trial, and detect noncompliance, with research protocols, which may include performance and enrollment goals. The present invention uses algorithms and decision rules to provide an empirical approach for predicting different types of participant noncompliance with research protocols. This actuarial approach to determining participant noncompliance with clinical trial protocols is consistent with empirical research demonstrating the superiority of actuarial prediction of human behavior as compared to subjective clinical judgment. According to an alternative embodiment of the invention, a portable electronic device is used to query and collect data from one or more clinical trial participants to determine compliance and/or noncompliance. For example, the present invention may be used to record, assess and/or predict how well a given clinical trial site or other participant does at adhering to clinical trial protocols or achieving the goals of the clinical trial, for example, achieving enrollment targets. As another example, the present invention could be used to record or predict how well a subject in a clinical trial has adhered to or will adhere to the requirements of the clinical trial.

As used herein "clinical trial" refers to a broad range of data collecting activities, including studies directed to monitoring of one or more conditions within a clinical trial group of subjects. One such example includes drug trials involving humans.

As used herein, "protocol" or "clinical trial protocol" refers to plan for a clinical trial, including set procedures for performing the clinical trial, and performance goals, such as enrollment targets, for the clinical trial.

As used herein "compliance" refers to a parameter indicative of the quality and/or performance of a participant in a clinical trial, generally indicated by adherence to protocol, such as adherence to set procedures in a clinical trial, adherence to or achievement of certain goals of a clinical trial, such as enrollment goals, and/or any other parameter indicative of overall performance of a participant in a clinical trial.

As used herein "clinical trial participant" or "participant" refer to any person, place or thing involved in a clinical trial, including, but not limited to, doctors, nurses and other medical professionals, administrators of a clinical trial, investigators, study coordinators, data and site monitors, data collectors, subjects in a clinical trial, clinical trial monitors, as well as the overall clinical trial site, sponsoring pharmaceutical company and contract research organizations that provide training for clinical trial sites and personnel. Participants may collect data from a clinical trial, provide data during a clinical trial, record data during a clinical trial, administer instructions to other participants in a clinical trial, enroll subjects to participate in a clinical trial, and/or perform any other task associated with the procedures of a clinical trial. Clinical trial monitors are generally personnel, such as from a sponsoring pharmaceutical company, or of a third-party contract research organization, which monitor the activities of the research sites, including the activities of other clinical trial participants.

As used herein "subject" refers to any participant in a clinical trial about whom clinical data is collected, whether or not the subject has any relationship to a doctor or other health care provider.

"Trial data" or "clinical trial data" refers to data gathered for the principle purpose of the clinical trial. For example, trial data would include pain levels experienced by subjects in a pain medication clinical trial or craving levels in an anti-smoking medication clinical trial.

"Evaluability data" or "compliance data" or "compliance information" is data indicative of performance and/or compliance of a participant with clinical trial goals and procedures (i.e., protocol). Historical compliance data is any data collected at any point in time prior to analysis, and may be collected during an earlier clinical trial, or earlier in the same clinical trial for which an analysis of the compliance data is conducted. Compliance data may relate to the circumstances under which the trial data was collected or other data pertaining to characteristics, including the quality, of the trial data or other evaluability data. Some examples include overall performance, timeliness, consistency with other collected data, data quality (e.g., number of checks and edits, audit reports and so on), proximity of the data to an expected data range, completeness of the data, enrollment numbers in the clinical trial, enrollment targets and achievement of enrollment targets, previous compliance information for a particular site, such as historical tendency of a site to reach targeted enrollment goals, produce useful, compliant data, consistency of instructions or training given to participants with model instructions or training, and monitoring provided during the performance of a clinical trial.

"Historical protocol data" includes data specifying the research protocol of earlier clinical trials or from earlier within the same clinical trial. Historical protocol data is not limited to data from an entirely different trial, but also includes an application to an interim analysis to an on-going trial (e.g., long-term safety trial). As used herein, research protocol may include research goals, such as a target enrollment level in a clinical trial. Examples of historical protocol data can include questions posed to subjects, frequency of prompting of a subject during various times of the day or week, time allowed for subjects to respond to questions, requirements of subject behavior, conditions mandating removal of a subject from certain statistical analyses or removal as participant in the clinical trial, demands or expectations imposed upon the sites, targets for subject enrollments, and so on.

As used herein "portable electronic device" refers to any electronic device that can be adapted for use by a subject and/or clinical staff for viewing and/or inputting information. Preferably, the portable electronic device will also have a visual, audible or tactile alarm to gain the attention of the subject. For example, a pager having a vibration alarm may be used as a portable electronic device. Further examples include pagers with audible alarms and/or text messaging capabilities, a laptop computer or a cell phone. Preferably, according to the invention, a portable electronic device will be a handheld computer provided with a display and a data input feature, such as a touch-sensitive screen, or buttons to enable a subject to respond to questions posed on the display or to input unsolicited information. Examples of such portable electronic devices include the Palm Pilot by Palm, Inc or Windows-based devices running Pocket PC from Microsoft Corporation. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem and/or a network, such as a LAN or the Internet.

According to an embodiment of the present invention, a system is provided as shown in FIG. **1**. A processor **10** is provided and is adapted to communicate with at least one database **20**. As discussed below, the database preferably stores data related to participant compliance and associated research protocols. An input device **30** is also provided to allow the subject or another person to provide input to the processor **10**. The input device **30** may be a keyboard, a modem or other such device adapted for communication with the processor. An output device **40** is also preferably provided to receive and display information from the processor **10**. Examples of output devices **40** include a printer and a monitor.

In one embodiment of the invention, a portable electronic device **50** is provided and is selectively operatively coupled to the processor **10**. The portable electronic device **50** can also include a processor and may serve as an alarm, an input device, an output device, and/or a database. One example of a portable electronic device is a Palm Pilot by Palm, Inc, as described above. However, a portable electronic device is not a necessary component of the invention.

According to an embodiment of the invention, a flow chart illustrating the method of the present invention is set forth in FIG. **2**. First, relevant participant compliance data, and associated protocol data, reflecting participant compliance with research protocols in clinical trials, is provided, step **110**. The compliance data may be from an earlier clinical trial, or be taken at an earlier point in time during the same clinical trial for which the analysis is performed. Optionally, only participant compliance data may be provided, as some application of the present invention may not require knowledge of associated historical protocol for use of the participant compliance data. For example, analysis of response times to questions may not require knowledge of the maximum permissible time for subjects to answer questions in earlier

clinical trials or analysis of enrollment numbers may not require knowledge of previous enrollment targets.

Participant compliance data and associated protocol data is preferably stored in one or more databases **20** and may be identified from earlier clinical trials and/or earlier activities of a current clinical trial. An output of the present invention preferably includes a database to provide participant compliance data and associated protocol data for later use by the invention.

For compliance data regarding a subject in a clinical trial, the compliance data and associated protocol data is preferably specific to the type of condition or medication that is the focus of the clinical trial. For example, if the clinical trial relates to a cardiovascular condition, the data preferably relates to subject compliance with protocols in cardiovascular clinical trials. Likewise, if the clinical trial relates to a cardiovascular medication, the data used in the present invention will preferably relate to subject compliance with protocols in cardiovascular clinical trials. It is also within the scope of the invention to optionally include subject compliance data and associated protocol data obtained from an earlier phase of the clinical trial into the compliance data of the present invention. Alternatively, the subject compliance data and associated protocol data may not be related to the type of condition or medication that is the focus of the clinical trial.

For overall compliance data regarding a particular clinical trial site as a participant, the compliance data and associated protocol data may be specific to the clinical trial site's ability to produce usable, compliant data. For example, to identify sites that traditionally enroll large numbers of participants, the compliance data provided and used in step **110** may relate to enrollment levels and/or the historic ability of the particular clinical trial site to reach enrollment targets. To identify sites that tend to produce the most accurate data, the compliance data provided and used in step **110** may relate to how compliant these sites were in previous clinical trials or earlier in the same clinical trial with respect to training, subject compliance, and regular trial monitoring. In addition, the compliance with instructions and research protocol of individual subjects participating in a clinical trial at a clinical trial site may be used to evaluate the quality of that particular clinical trial site. The historical data on site or personnel compliance may be specific to that site or person, or may relate to historical performance of a class of sites (e.g., contract research organization sites, independent sites, small sites, large sites, sites grouped by geographic regions, and so on) or persons (e.g., particular medical specialties, seniority and experience in clinical trials, tenure at the site, or other factors).

For compliance data for a monitor of a clinical trial, the compliance data may relate to how well the monitor complied with the monitoring procedures of the clinical trial.

For compliance data for an administrator of a clinical trial, the compliance data may relate to whether the instructions given to a subject regarding the collection of data were consistent with model instructions.

For compliance data relating to a contract research organization, the compliance data may related to the quality of the training for the clinical trial sites and personnel provided by the contract research organization.

The compliance data obtained in step **110** may be any parameter indicative of the performance of a particular participant in a clinical trial and are not limited to the above-described examples.

Next, at least one algorithm representative of the participant compliance data is generated by quantitative analysis of the compliance data, step **120**. Preferably, multiple algorithms are generated. The present invention involves the application of statistical and other quantitative methods to screen existing research data for markers of, e.g. variables related to, noncompliance with research protocols, including research goals. Preferably, the participant compliance data is also reviewed to exclude invalid data. For example, data reported by one subject that appears to be well outside a range established by all other subjects can indicate invalid data.

Examples of various types of data that may be collected according to an embodiment of the invention to determine the quality of a participant by determining the compliance of the participant with clinical trial protocol may also include variables that may represent 'non-intuitive' predictors such as: gender of the subject or other participant about whom data is collected, disease severity, the time of the year, and the day of the week, location of the clinical trial site, demographic profile of the community surrounding a clinical trial site, experience and/or education level of the personnel participating in the clinical trial, salary level of employees of the clinical trial site, character of the clinical trial site (i.e., public university, private university, private doctor's office, research center, corporation whether the clinical trial site and/or participants have run any research in the past, how many clinical trials over what period of time, whether the investigator is an SAB member of the sponsor, and so on), number of employees involved in running a particular clinical trial or other data useful for predicting compliance and, therefore, overall performance. Additional prediction factors may also include characteristics of the research protocol, such as the nature of the subjects being recruited, the number of patients being recruited, the duration of the study, and may also include contractual aspects of the study, such as incentives for enrollment, payment per completed subject, and so on.

Quantitative analysis methods are used to distinguish, identify, and predict instances of good and poor compliance and/or instances of valid or invalid data. The quantitative analysis methods of the present invention may include, but are not limited to, application of a variety of statistical and data mining techniques, such as logistic regression, discriminant function analysis, classification and regression trees, neural networks, and multiple linear regression to screen existing data and derive algorithms to identify markers of noncompliance with research protocols.

Logistic regression analyses use dichotomous and continuous variables to predict dichotomous outcome variables. For example, dichotomous outcome variables can indicate "completed" or "failed to complete" a clinical trial monitoring protocol. Discriminant function analysis relates a categorical criterion variable to dichotomous or linear predictors. Classification and Regression Trees (CART) use binary recursive partitioning to identify unique groups of participants, such as, for example, subjects failing to complete the clinical trial protocol and subjects completing the protocol with minimal corrective feedback regarding their compliance with the clinical trial protocol, or sites that met recruitment targets versus those that did not. Neural network approaches to pattern recognition examine data for patterns and classify certain patterns of data based on the probability that they lead to a given outcome. Multivariate Regressive Splines (MARS) build flexible regression models, including interactions, by fitting separate splines to distinct intervals of the predictor variables.

Other nonparametric and parametric statistical approaches can also be applied to the prediction of participant noncompliance with clinical trial protocols, including clinical trial goals.

A variety of predictor and criterion variables can be used in the present invention. For subject compliance, predictor vari-

ables can range between basic demographic characteristics, such as, for example, gender of a subject or location of a clinical trial site, to specific clinical trial compliance related variables, such as, for example, mean latency to respond to an audible prompt from an optional portable electronic device or enrollment levels at a clinical trial site. Similarly, criterion variables can range from subtle, such as, for example, missing some percentage of portable electronic device prompts or failing to provide sufficient instructions to a subject, to severe noncompliance, such as, for example, failure to complete the clinical trial protocol or failure to enroll a single subject for a clinical trial. For detection of fraudulent entries, example predictor variables could include the speed or rate of entries, or an implausible or statistically unlikely pattern of answers to a set of assessment questions.

The present invention allows for complex, non-intuitive interactions among multiple variables to optimally predict participant compliance with clinical trial protocols, including clinical trial goals. That is, the markers or variables used to predict noncompliance may or may not, in and of themselves, be related to noncompliance. Algorithms may rely on different variables for different subgroups. For example, subgroups can include, but are not limited to, men and women, older or younger subjects, subjects late or early in the clinical trial, clinical trial sites associated with universities and clinical trial sites associated with corporations, clinical trial sites in cities and clinical trial sites in rural areas, clinical trial sites that provide extensive training and clinical trial sites that provide minimal training, clinical trial sites run by doctors and clinical trial sites run by other medical professionals, large studies or small studies, studies with enrollment targets and/or incentives versus those without such, and so on. The algorithms may also identify different combinations of variables working only in tandem. Thus, the variables alone may not be directly, simply, or obviously related to noncompliance. The algorithms of the invention may use complex and nonintuitive combinations of predictors to predict subject noncompliance with clinical trial protocols. The invention also allows context-specific algorithms to maximize predictive utility. That is, different algorithms can be derived for different groups of subjects, such as, for example, subjects with cardiovascular or central nervous system diseases, or from different kinds of sites, such as those that are part of a Contract Research Organization versus those that are not. As a result, the present invention avoids assuming that any given set of variables will be equally predictive of clinical trial noncompliance for all types of conditions or diseases or for all types of participants.

According to an embodiment of the invention, the present invention also provides for novel quantitative analyses to be incorporated into the development of algorithms to further improve their predictive validity. Specifically, the algorithms can be subject to continuous improvement as more data become available for analysis, either within an individual clinical trial or accumulating across clinical trials.

According to a further embodiment of the invention, algorithms can be used to determine appropriate feedback to subjects, research staff, sites, and sponsors regarding compliance with the protocol. For example, a computer program can implement decision rules based on these algorithms, and automatically determine appropriate feedback or action by the personnel involved in conducting or overseeing the clinical trial.

An advantage of the present invention is that, because the algorithms and decisions are based on formal, empirical, and quantitative criteria, they remove the subjective element in these decisions, which in turn minimizes the potential for bias. Another advantage is that the statistical algorithms can sometimes identify relationships that would not be evident to ordinary observation and/or relationships based on unintuitive variables or combinations of variables.

The above and other advantages provided by the disclosed invention include provisions for the application of these algorithms within existing and yet to be developed processes for giving systematic feedback to subjects, research sites, and clinical trial sponsors conducting clinical trials using clinical trials.

Once the one or more algorithms of the invention have been derived from analysis of existing data, the algorithms can be translated into specific decision rules, step **130**. Decision rules are essentially reformatted algorithms that can be applied to current participant compliance data to determine whether action is needed, step **140**. When using the compliance data to identify participants likely to produce sufficient, reliable results in a clinical trial, the action taken in step **140** may comprise selecting that participant for a prospective clinical trial or avoiding the participant for future clinical trials based on the production of historically non-compliant data. The action taken in step **140** may alternatively comprise dismissing the participant from an ongoing clinical trial or any other suitable action that would be influenced by the compliance or noncompliance of a participant in a clinical trial.

Decision rules may determine a threshold of compliance or a threshold of noncompliance. The thresholds may be defined empirically and/or algorithmically. In addition, the thresholds used to determine compliance and/or noncompliance to give an indication of performance may be defined by the sponsors of the clinical trial, the vendors, an independent organization or other suitable participant. Optionally, a decision rule may identify a spectrum of noncompliance, from minor noncompliance needing only corrective feedback, to significant noncompliance requiring removal of a participant from the clinical trial. Decision rules may be based on the specific dependent variable used to derive the algorithm or may be based on one or more differing variables.

For example, a subject who, within the first two days of the clinical trial, does not respond to more than 20% of prompted inquiries and either suspends prompting more than once or indicates he/she is napping more than once may be identified as noncompliant, i.e., likely to fail to comply or failing to comply with the research protocol. As another example, subjects who suspend prompting at least twice, and whose total time of such suspension exceeds 2 hours, might be determined to be likely noncompliant, regardless of their overall performance. In another example, administrators who fail to provide proper training to subjects on multiple or a certain number of occasions (determined by the algorithm) may be judged or determined to be noncompliant. A clinical trial site that fails to reach enrollment targets on a given number of occasions might also be determined to be noncompliant, regardless of the overall performance of the site. For purposes of illustration, one sample decision rule may be stated as:

> Display noncompliance remediation message to clinical staff if: [0.32 (ratio of missed random prompts)+0.45 (mean number of minutes spent time delaying assessments per day/100)+0.80 (mean number of hours spent in sleep each night over past 7 days/10)]>1

where if noncompliance is determined by this decision rule, an action, such as sending a specific message to the clinical staff is recommended. For example, in the present example, the message "Subject is not following the protocol as

required, resulting in substantial missed assessments. Call subject." may be determined to be the appropriate action.

According to an embodiment of the invention, criteria for identifying a participant as noncompliant with the research protocol need not overlap with criteria developed for determining whether to drop a participant from the clinical trial or exclude data related to or from that participant from the clinical trial results. For example, the decision rule(s) related to dropping a subject from the clinical trial might be based on failed responses to audible prompts rather than on suspension of prompting.

Typically, a decision rule specifies what type of action is required and may provide specific action details. Action types include corrective, affirmative and anti-fraud actions. Action details may include the content of a message to be provided to a subject, clinical staff monitoring staff, or sponsors.

Decision rules may be translated from algorithms that identify patterns of non-compliance data that are harbingers or leading indicators of later, more serious, non-compliance. This would allow early action to be taken based on these indicators. Such decision rules would typically be in the form of contingencies or conditions based on early compliance indicators.

Optionally, translation of algorithms to decision rules may involve human input or additional factors. For example, balancing the impact of a decision rule against the focus of the clinical trial may result in an alteration of the decision rule. For example, if subjects' heart rates are being monitored, frequency of prompting or loudness of reminder alerts may be minimized so as not to artificially raise subject heart rates. Also, clinical staff may alter decision rules based on their assessment of external factors outside of the scope of the quantitative analysis. An example may include providing more alerts to clinical staff instead of directly to subjects to provide more interaction between clinical staff and the subjects.

A decision rule may also be used to predict which participants, in particular which subjects, will fail to complete a clinical trial protocol and therefore will fail to produce useful data. The decision rule may alternatively or also identify participants that have already produced nonusable, inaccurate and/or insufficient data due to noncompliance earlier in the clinical trial or in an earlier clinical trial. Therefore, a decision to rule to drop the participant from the clinical trial, or to work to improve participant performance, can be made at an early time. In addition, a decision to avoid using data from a particular participant, such as a clinical trial site, altogether made be made. By providing those conducting a clinical trial with early feedback regarding participant noncompliance with a research protocol, the present invention improves clinical trial data quality and may potentially save both time and money by either improving the compliance of potentially noncompliant participants or excluding unimprovable noncompliant participant early in a clinical trial or before any resources are wasted on beginning a clinical trial.

The decision rule may determine an action based solely on past noncompliance, without requiring an explicit prediction of future compliance. For example, if an analysis of compliance data indicates that a participant has failed to comply with clinical trial protocol, the decision rule based on the analysis may instruct removal of the participant from an ongoing clinical trial.

According to one embodiment of the invention, the principles used to predict compliance and/or fraud may be applied to data as it comes in from a trial to determine the accuracy and/or compliance of the data with research protocol. The prediction may be made from data other than strict "compliance" data, but may include clinical data in the trial.

The generation of a fraud detection algorithm can take many forms. The psychometric properties of the scale itself could be used to identify potentially fraudulent responses. For example, according to one embodiment of the invention, item response theory uses known properties of individual items within an assessment to estimate the probability that an observed pattern of responses is valid. Therefore, a subject answering yes to the question "My headaches are completely debilitating" has a low probability of also answering yes to the question "My headaches are a minor inconvenience" such that observing this pattern of responses could be indicative of fraud. Inconsistencies with trial data may also indicate the manufacture of data by a clinical trial site or other participant. In another example, a clinical trial having a subject indicating that minimal training or monitoring was provided by clinical trial staff has a low probability of the staff indicating that extensive training and/or monitoring was provided.

According to a further embodiment of the invention, the detection of fraudulent or invalid entries in participant-supplied data may be performed similarly to the methods described herein. For example, the analysis could be based on statistical properties of the responses themselves. Thus, as an example, analysis might indicate that when the standard deviation across subject responses on a particular questionnaire are less than 1.0, fraudulent or invalid completion (whether by the subject or by other trial participants) is highly likely.

The content of subjects' responses could optionally be used as a source of data for the fraud detection algorithms if the responses are invariant or relatively invariant. For example, a subject answering 'yes' to all questions, even when the logical content of the questions would suggest some alternating pattern of appropriate responses may indicate fraud. Fraud from other participants may be similarly detected. For example, the invention may identify the manufacture of data by a clinical trial site, meant to deceive the organizers or sponsors of the clinical regarding the number of subjects participating in the clinical trial.

Analysis of fraud could also be based on particular combinations of responses. Thus, subjects who answered that they took pain medication five or more times daily, but who elsewhere indicated either that pain severity was 4, on a scale of 1 to 10, or that pain frequency was 'infrequent' or 'rare', might be flagged as cases likely to be invalid. The response patterns determined to represent potentially fraudulent data need not be logically inconsistent or intuitively invalid. Rather, they are determined to represent potentially fraudulent data based on statistical analysis comparing valid and invalid response profiles. Therefore, questions posed to subjects or other participants in a clinical trial can be tailored to provide opportunities for the subject to contradict, or appear in disagreement with, responses to earlier questions.

In an alternative embodiment, the posing of questions providing opportunities to contradict earlier responses can be interactive. For example, further questions providing opportunities to contradict earlier responses can be posed only if a response to a question appears unusual or if a decision rule indicates earlier indications of potential fraud.

As a further example, the time required for a subject to respond to items could be the foundation for the generation of fraud detection algorithms. For example, evaluability data could be used to estimate the mean length of time subjects take to respond to certain items. In such an example, response latencies less than or more than two standard deviations below those norms could be the basis of identifying the

responses as potentially fraudulent. For example, if a question contains 25 words and subjects take an average of 8 seconds to answer the question, responses of less than 1 second could be identified as potentially fraudulent.

Alternatively, the portable electronic device could capture certain ecological data such as temperature or airborne particles, or physiological data, such as concurrent heart rate, suggestive of a particular location, subjective, or physical state, which is inconsistent with the subject's responses, suggesting possible fraud.

In an alternative embodiment of the invention, participants can be included in the clinical trial for the purpose of providing fraudulent data. For example, in a group of 100 subjects, 20 subjects may be asked to provide fraudulent data. By having such fraudulent data among data provided by the subjects, the quantitative analysis of the present invention can be used to ensure the resulting algorithms and decision rules detect the known fraudulent entries. In the event other subjects are also fraudulently recording data without the knowledge of the clinical staff, the algorithms and decision rules will likely also detect such unknown "spontaneous" fraudulent activity.

Each of the above variations for detection of fraud can be used according to various embodiment of the present invention individually, sequentially or in combination.

According to a preferred embodiment of the invention, the system of the invention for automated processing of data collected via a portable electronic device is provided. In this embodiment, the portable electronic device or system is designed to prompt a participant for information and/or collect information as recorded by the participant without prompting. Preferably, each subject in the clinical trial is provided with a portable electronic device. The portable electronic device is preferably used to collect compliance-relevant variables, such as the number of data entry episodes, missed data entry occasions (e.g., instances where the portable electronic device prompts for data, but the subject fails to respond). A database of these variables is preferably processed according to the decision rules to guide the actions of the portable electronic device as described in detail in the copending patent application titled "System for Clinical Trial Subject Compliance", Attorney Docket No. IVQ-002.

The portable electronic device for each subject is also preferably adapted to communicate with another computer to allow the clinical staff to consolidate the data from all subjects in the clinical trial into one location for review or processing. Preferably, the portable electronic device will also be adapted to communicate with at least one other computer via a wireless connection or via a wired connection, including the use of a modem and/or a network, such as a LAN or the Internet. For example, by the use of the Internet or a dial-up modem connection, a subject may submit information from the portable electronic device to the clinical staff from the subject's home.

In another embodiment, a portable electronic device or a computer is adapted to communicate with clinical trial equipment used for measuring, monitoring, controlling or recording data or a process of the clinical trial. Examples of such processes include administration of medication or monitoring of heart rates. The portable electronic device or a computer preferably automatically records desired data for incorporation in the clinical trial data or compliance data.

In another embodiment of the invention, a paper form, such as a case report form, can be used by the subject or other participant to record data. The data can then be entered into a database by the use of a portable electronic device or other computer at an appropriate time. Examples of case report forms include hand-written forms and forms that allow for machine readable marks to be made, enabling automated scanning of the case report forms during entry of the data into a computer.

In an alternative embodiment of the present invention, the methods of the present invention may be incorporated in instructions recorded on a medium suitable for use in an electronic device, such as a computer, computer network server or a portable electronic device. The medium can include, for example, a hard disk, RAM medium, diskette, CD-ROM or other optical or magnetic storage medium. The instructions can optionally be stored on a server that can be remote from the subject or clinical staff member.

According to an embodiment of the invention, the server can provide data to be displayed. Data may be displayed at the server itself or be transmitted to another location, such as via hardwired or wireless access to the server, including a LAN or the Internet. The data can be processed to provide a graphical display to interested parties. Examples of those who may be interested in viewing the graphical representation of the compliance data include a site coordinator (who may be interacting with the subject), a clinical research organization (who may be responsible for study execution across a number of research locations), other agencies interested in the collection of the data, or the sponsor of the research.

According to another embodiment of the invention, the server can provide ongoing aggregation of data across participants to speed the time required to combine, clean, and make available final data.

In another embodiment of the invention, a compliance database, such as an Excel® database, may be compiled using compliance data collected from one or more clinical trials. The compliance database may be used to predict compliance of any clinical trial participant in a future clinical trial, predict continued compliance in an ongoing clinical trial and/or identify noncompliance in a clinical trial. The compliance database may be used by sponsors of a clinical trial to select participants that will most likely yield accurate, useful results without wasting resources.

The compliance database may contain many different metrics on the participant performance, as described above. For example, for particular clinical trial sites, the compliance data in the database may list the historic ability of each site to reach enrollment targets, how compliant each sites was in previous clinical trials with respect to training, subject compliance, and regular trial monitoring and other data indicative of compliance and therefore overall performance.

In this manner, a sponsor of a clinical trial may identify highly qualified participants, such as clinical trial sites that historically produce adequate, accurate and reliable data, for conducting a clinical trial, and avoid wasting resources on participants that will not tend to produce usable results, such as non-performing clinical sites.

For example, the performance of targeted clinical sites in previous clinical trials may be tracked according to an embodiment of the invention in several different ways. The resulting database allows for statistical analysis and identification only those clinical sites that have been able to meet their enrollment targets and excel in compliance with research protocols in other clinical trials. Selected clinical sites may then be ranked in a given therapeutic category to identify the premier clinical sites that are most likely to succeed in a proposed clinical trial.

These examples are meant to be illustrative and not limiting. The present invention has been described by way of example, and modifications and variations of the exemplary embodiments will suggest themselves to skilled artisans in this field without departing from the spirit of the invention. Features and characteristics of the above-described embodiments may be used in combination. The preferred embodiments are merely illustrative and should not be considered restrictive in any way. The scope of the invention is to be measured by the appended claims, rather than the preceding

description, and all variations and equivalents that fall within the range of the claims are intended to be embraced therein.

What is claimed is:

1. A computer implemented method of determining noncompliance of a participant in a clinical trial, comprising the steps of:

providing historical participant compliance data;

generating at least one algorithm for determining participant noncompliance by quantitative analysis of the historical participant compliance data;

applying the at least one algorithm to determine participant compliance; and

outputting notice of noncompliance.

2. The method of claim **1**, further comprising the step of translating the at least one algorithm into at least one decision rule for use with a clinical trial.

3. The method of claim **2**, further comprising the step of selecting the participant for a prospective clinical trial based on the at least one decision rule.

4. The method of claim **3**, further comprising the step of dropping the participant from the clinical trial based on the at least one decision rule when the algorithm identifies the participant as noncompliant.

5. The method of claim **1**, wherein the participant is a particular clinical trial site, and the historical participant compliance data includes enrollment levels in previous clinical trials conducted by the particular clinical trial site.

6. The method of claim **1**, wherein the participant is a particular clinical trial site, and the historical participant compliance data includes achievement of target enrollment levels in previous clinical trials conducted by the particular clinical trial site.

7. The method of claim **1**, wherein the participant is a particular clinical trial site, and the historical participant compliance data includes data regarding the compliance of a clinical trial site with research protocols in previous clinical trials.

8. The method of claim **7**, wherein the data regarding compliance of a clinical trial site with research protocols relates to at least one of: training provided to subjects, monitoring of subjects during a clinical trial and compliance of subjects participating in clinical trials conducted by the clinical trial site.

9. The method of claim **1**, wherein the historical participant compliance data includes compliance data for subjects in clinical trials involving the participant.

10. The method of claim **1**, further comprising the step of storing the historical participant compliance data in a database.

11. The method of claim **10**, wherein the database stores historical participant compliance data for a plurality of participants in a clinical trial.

12. The method of claim **11**, wherein at least one algorithm for determining participant noncompliance by quantitative analysis of the historical participant compliance data is generated for each participant.

13. The method of claim **1**, wherein the historical participant compliance data is collected at an earlier point in time during the clinical trial.

14. The method of claim **1**, wherein the historical participant compliance data is collected during a previous clinical trial.

15. The method of claim **1**, wherein the participant is one of: a medical professional conducting the clinical trial, a subject in the clinical trial, an administrator of the clinical trial, an investigator, a study coordinator, a data collector, a clinical trial monitor, a clinical trial site, a sponsoring pharmaceutical company and a contract research organizations that provides training for clinical trial sites and personnel.

16. A computer implemented method of identifying a suitable clinical trial site for conducting a clinical trial, comprising the steps of:

providing a database storing historical compliance data for a plurality of clinical trial sites;

performing a statistical analysis of the historical compliance data for each clinical trial site to predict compliance in a future clinical trial; and

selecting a clinical trial site that is predicted to comply with research protocols.

17. The method of claim **16**, wherein the database ranks clinical trial sites according to a likelihood of compliance in a future clinical trial.

18. The method of claim **17**, wherein the database ranks clinical trial sites in a specific therapeutic category.

19. The method of claim **16**, wherein the historical compliance data includes enrollment levels for prior clinical trials.

20. The method of claim **16**, wherein the historical compliance data includes a ratio between a number of clinical trials conducted and a number of clinical trials in which target enrollment levels were achieved.

21. The method of claim **16**, wherein the historical compliance data includes compliance of subjects participating in previous clinical trials conducted by each clinical trial site with research protocols.

22. The method of claim **16**, wherein the historical compliance data relates to at least one of: training provided to subjects by the clinical trial site and monitoring of subjects during a clinical trial.

23. A computer implemented method of predicting success of a clinical trial involving a selected clinical trial participant, comprising the steps of:

providing historical compliance data from a clinical trial involving the clinical trial participant;

performing a quantitative analysis of the data to identify whether the participant is likely to produce data in compliance with research protocol in the future; and

identifying whether the participant is likely to produce data in compliance with research protocols in the future.

24. The method of claim **23**, wherein the historical compliance data is collected in a previous clinical trial from the clinical trial for which success is predicted.

25. The method of claim **23**, wherein the historical compliance data is collected at an earlier point in the clinical trial for which success is predicted.

26. The method of claim **23**, wherein the statistical analysis predicts compliance in a future clinical trial.

27. The method of claim **23**, further comprising the step of selecting the participant for a clinical trial based on the quantitative analysis.

28. The method of claim **23**, further comprising the step of dropping the participant from the clinical trial for which success is predicted based on the quantitative analysis.

29. The method of claim **23**, wherein the research protocol includes performance goals of a clinical trial.

30. The method of claim **11**, further comprising the step of ranking the plurality of participants based on a likelihood of each participant complying with protocols for a future clinical trail, determined by an algorithm associated with each participant.

* * * * *

CERTIFICATE OF SERVICE

I hereby certify that I caused to be electronically filed the foregoing Principal Brief of Appellant eResearchTechnology, Inc. with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the appellate CM/ECF system on September 6, 2016 and thus caused to be served on all registered counsel of record a copy of the same via the CM/ECF system.

September 6, 2016

/s/ Edward G. Poplawski
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CERTIFICATE OF COMPLIANCE
PURSUANT TO FED. R. APP. P. 32(a)(7)(C)

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains 12,704 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word in 14-point Times New Roman.

September 6, 2016

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